British Journal of Urology

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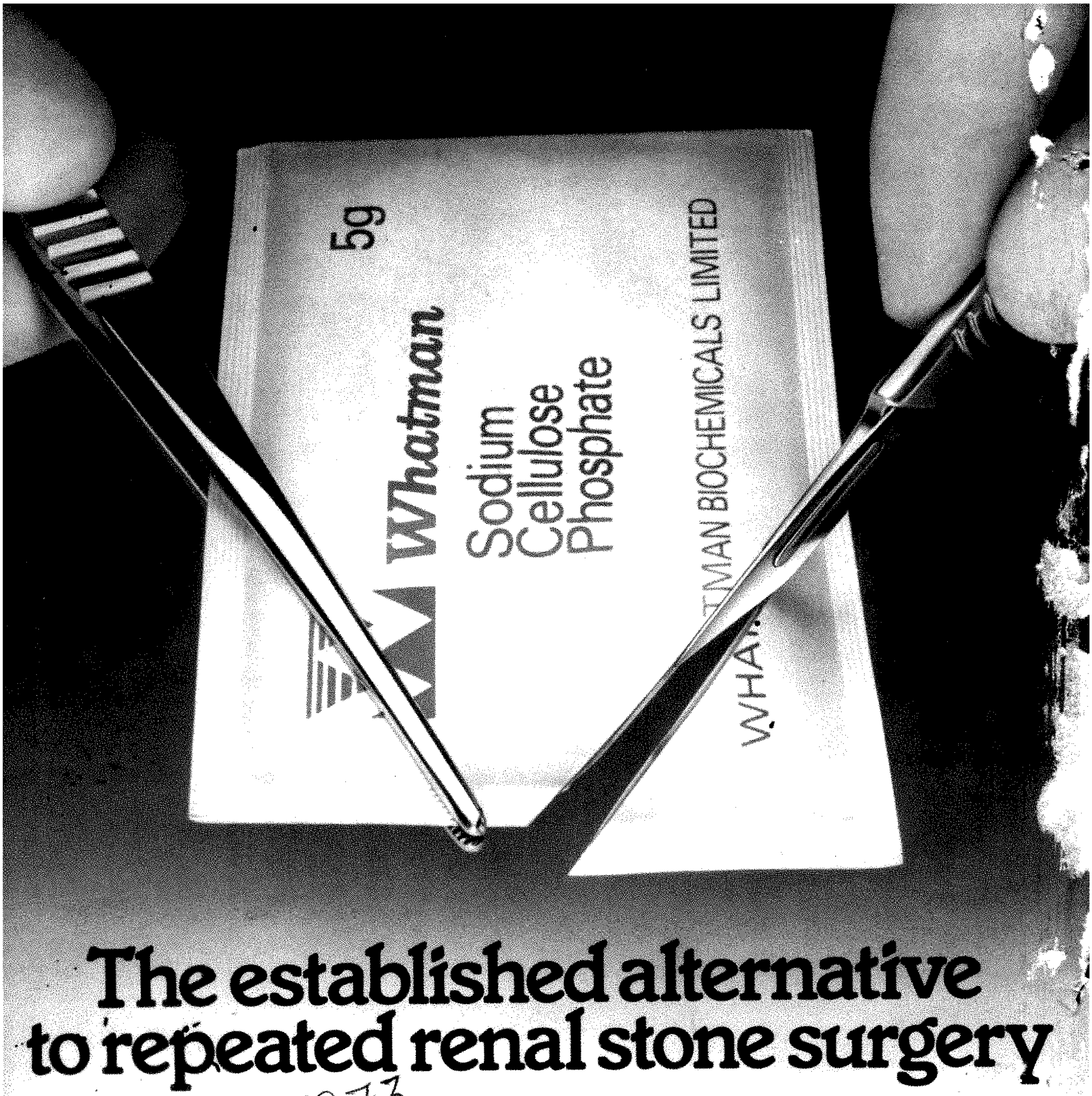

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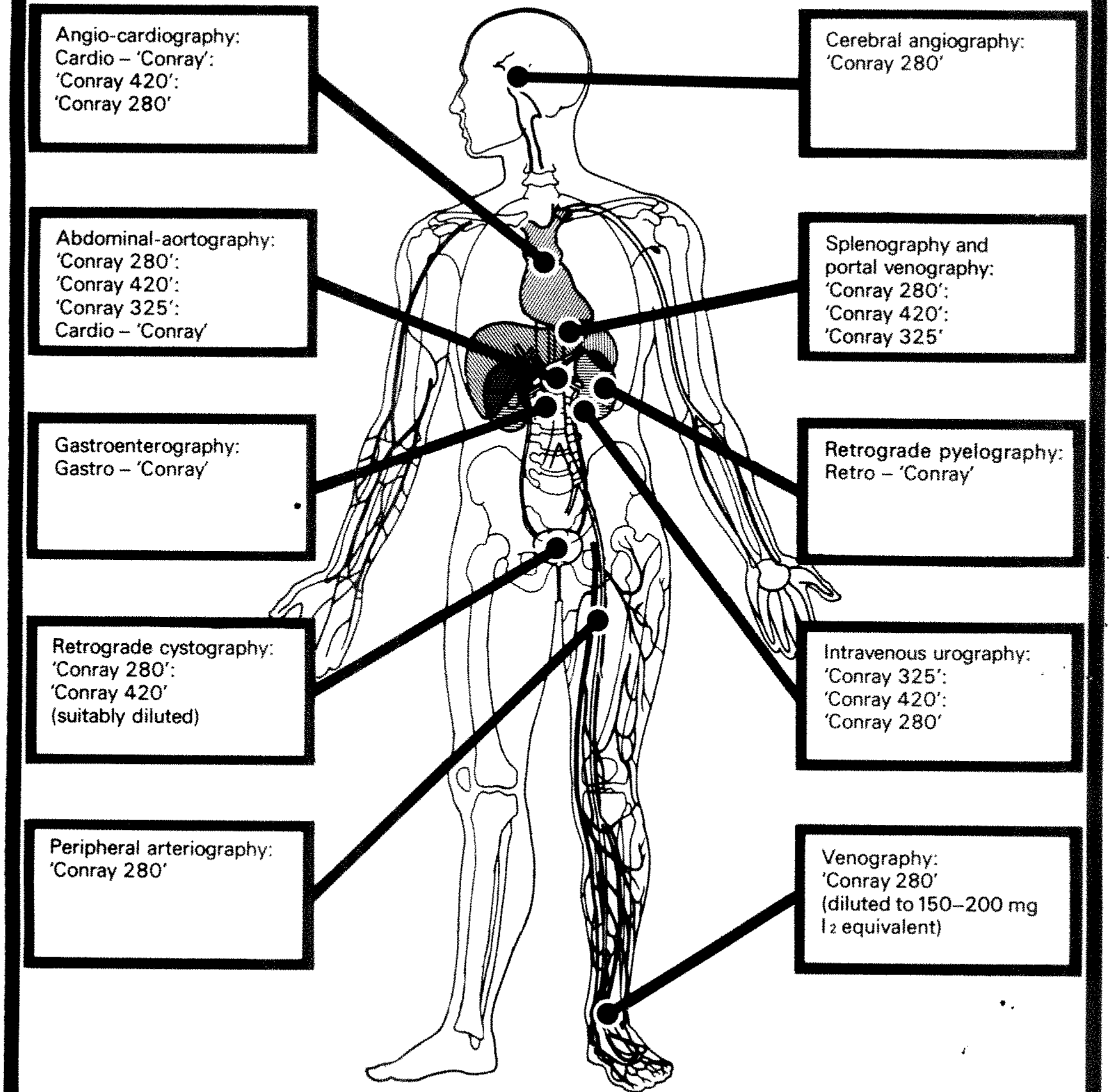

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PSYCHOSEXUAL DISORDERS: A Review *by* **M. T. Haslam,** *Clifton Hospital, York, England. Foreword by* **Martin Cole.** Following an historical review and classification of the various psychosexual disorders, this text explores topics related to sexual dysfunctions, including etiology and management of erective, orgasmic, and ejaculatory problems; vaginismus; and the sexual problems of handicapped people. Final chapters focus on the definition and treatment of homosexuality, transvestism, and transsexuality; primary patterns of sexual deviancy; medicolegal concepts; and problems of defining normal behavior. *'79, 212 pp., 13 il., $19.75*

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TRANSSEXUALITY IN THE MALE: The Spectrum of Gender Dysphoria *by* **Erwin K. Koranyi,** *Univ. of Ottawa, Ottawa, Ontario, Canada. Foreword by* **Ralph Slovenko.** *(3 Contributors)* A wide range of topics related to transsexuality in the male is herein explored, including the interplay of biological and psychological factors, sexual dimorphism, natural sex change, sexual roles in nature, and genetics and sexuality. Medicolegal considerations, surgical procedures, and hormonal and psychosocial treatments are also discussed. Although written for the transsexualism specialist, this book will be most helpful to students and practitioners in other areas of medicine as well as those in law and mental health. *'80, 192 pp., 31 il., 1 table, $17.50*

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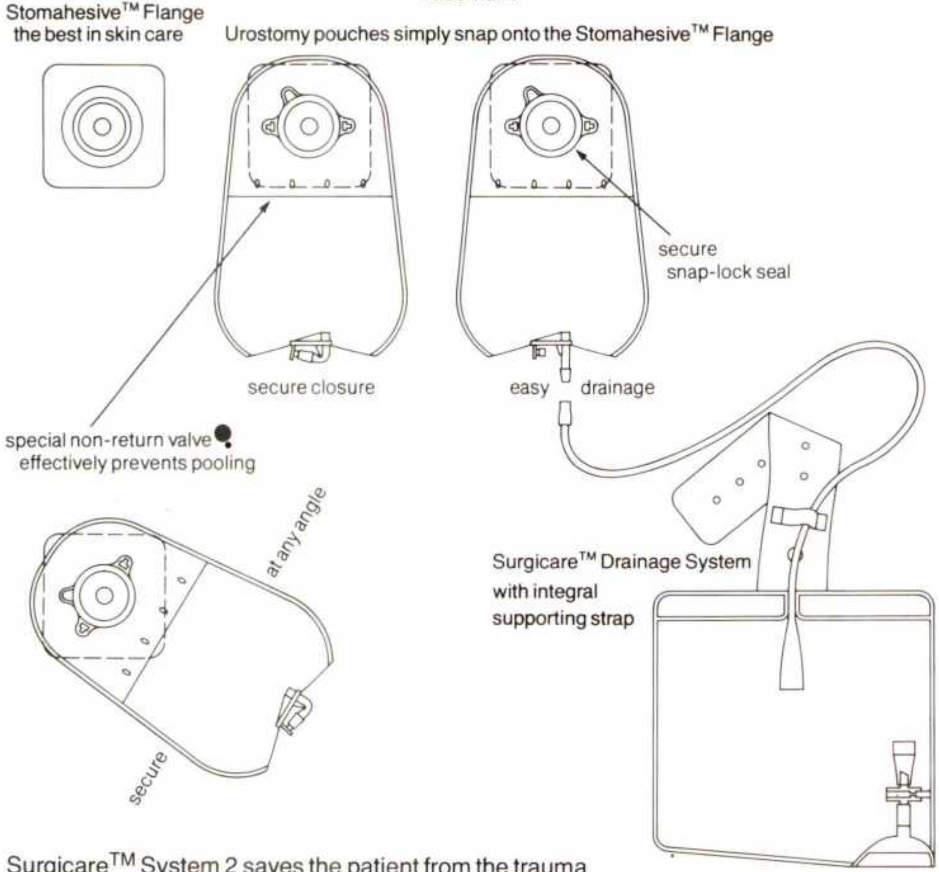
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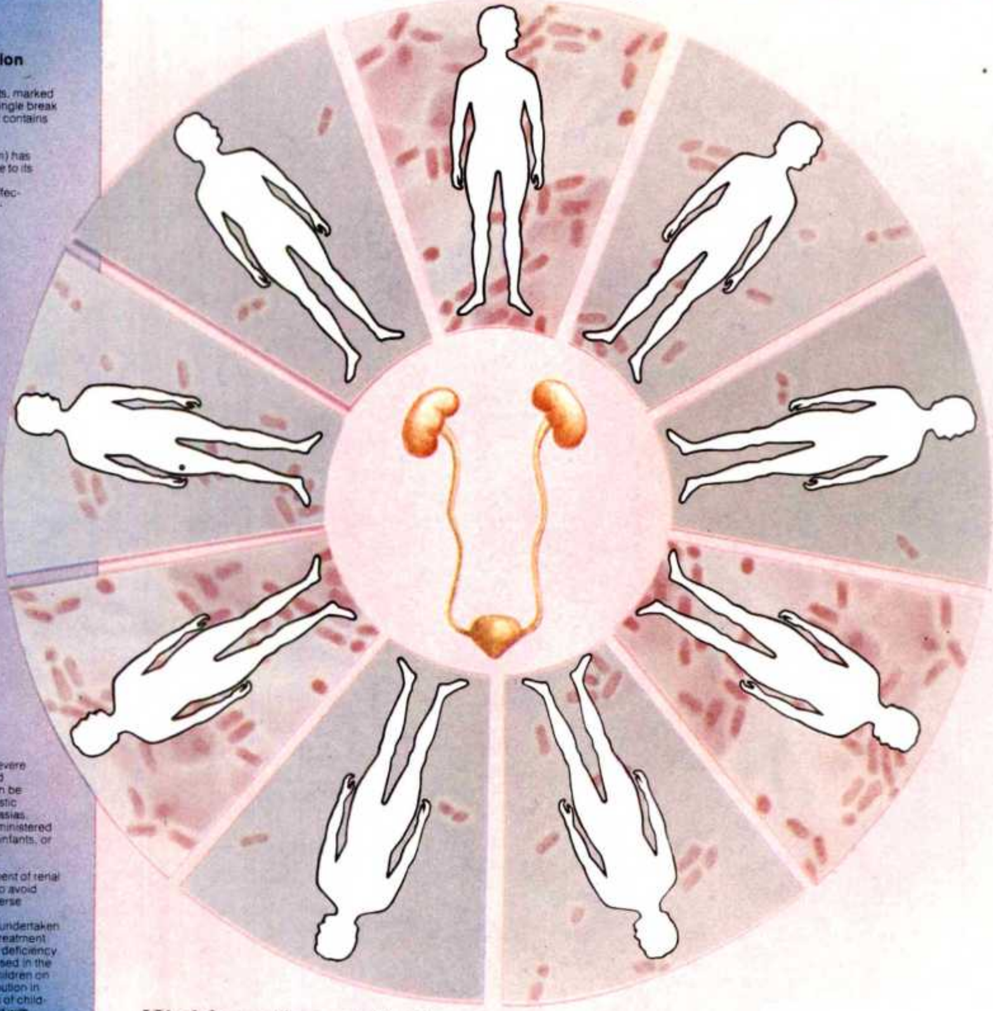

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Adults and children over 12 years of age:
Treatment of acute urinary tract infections: Two 100mg tablets twice daily.
Long-term prophylaxis of recurrent urinary tract infections: one 100mg tablet each night, before bed.
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Contra-indications:
Severe hepatic insufficiency. Severe renal insufficiency, unless blood trimethoprim concentrations can be monitored regularly. Megaloblastic anaemia and other blood dyscrasias. Trimethoprim should not be administered to pregnant women, premature infants, or children under 4 months of age.

Precautions:
In patients with marked impairment of renal function, care should be taken to avoid accumulation and resulting adverse haematological effects. Regular haematological tests should be undertaken in patients receiving long-term treatment and those predisposed to folate deficiency. Particular care should be exercised in the haematological monitoring of children on long-term therapy. The usual caution in prescribing any drug for women of child-bearing age should be exercised with trimethoprim. Trimethoprim is excreted in breast milk but is not contra-indicated for short-term use in lactating mothers.

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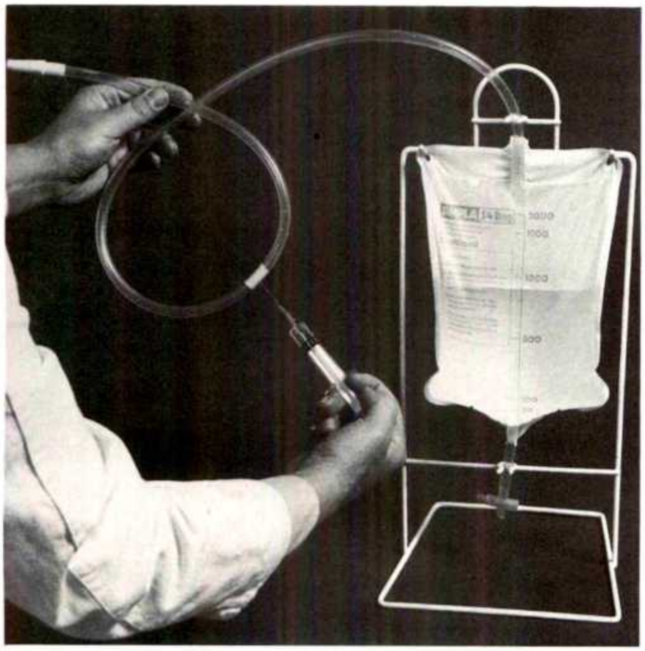

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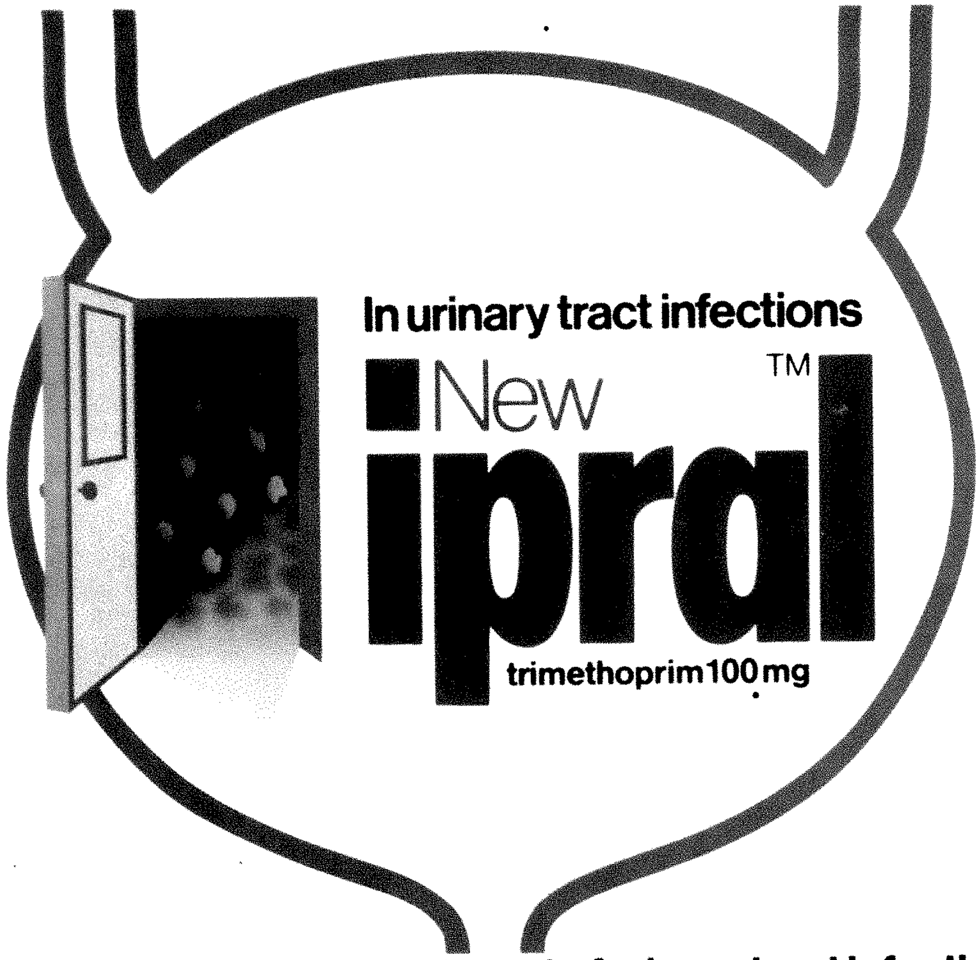

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References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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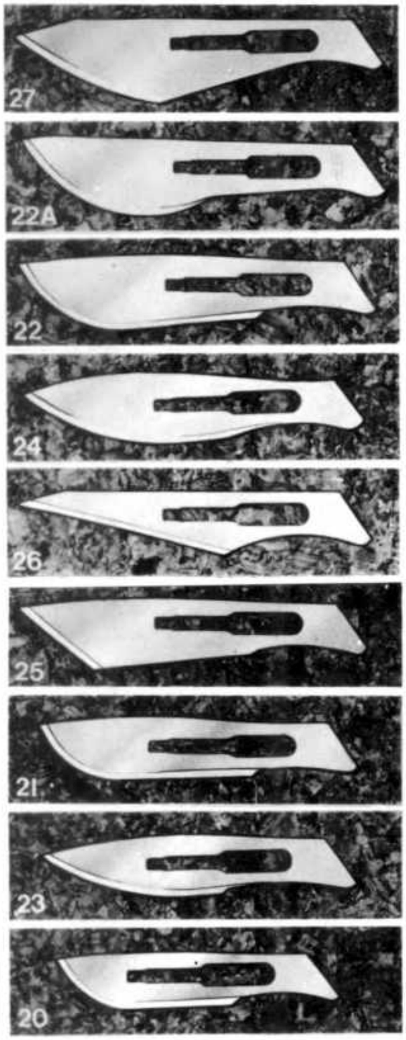

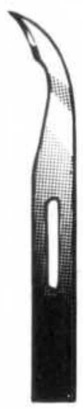

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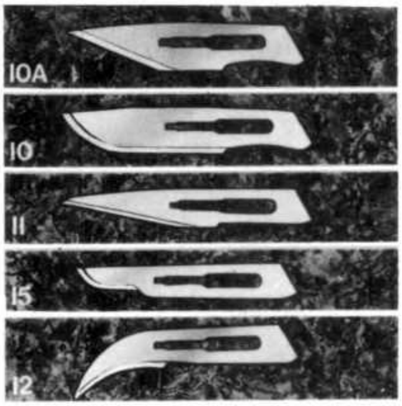

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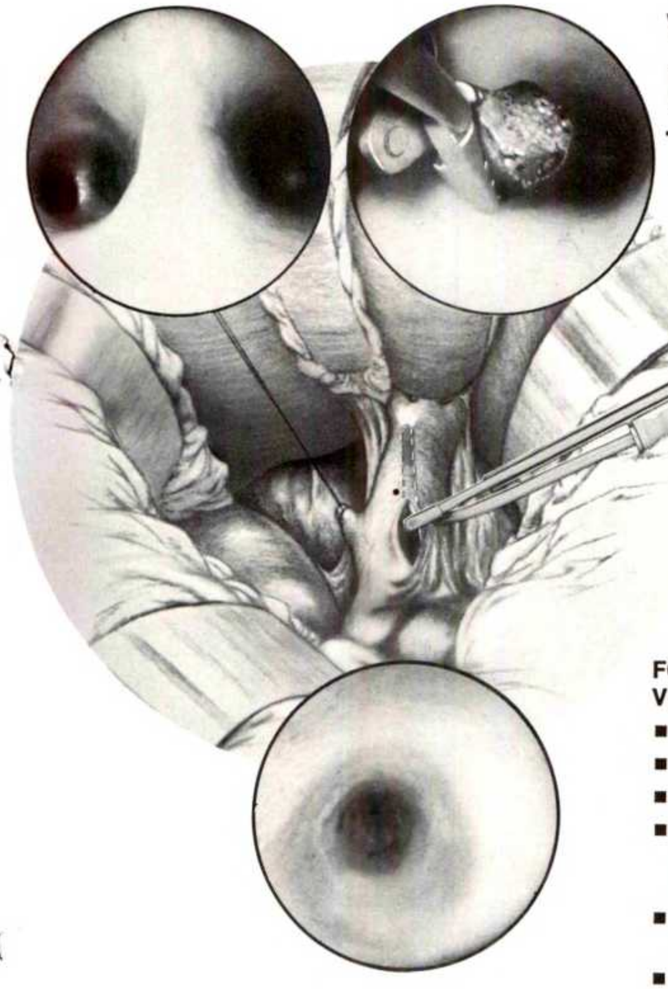

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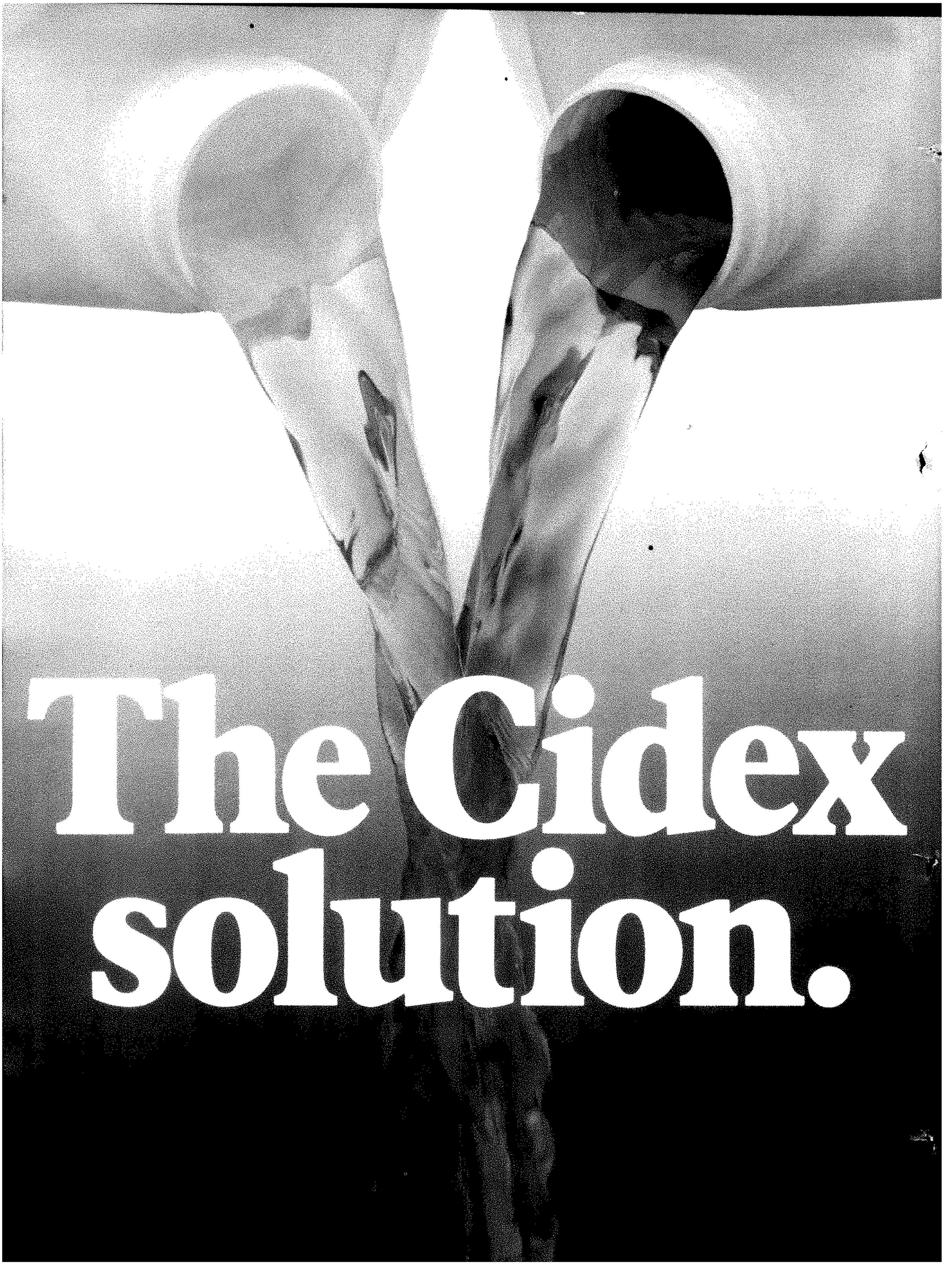
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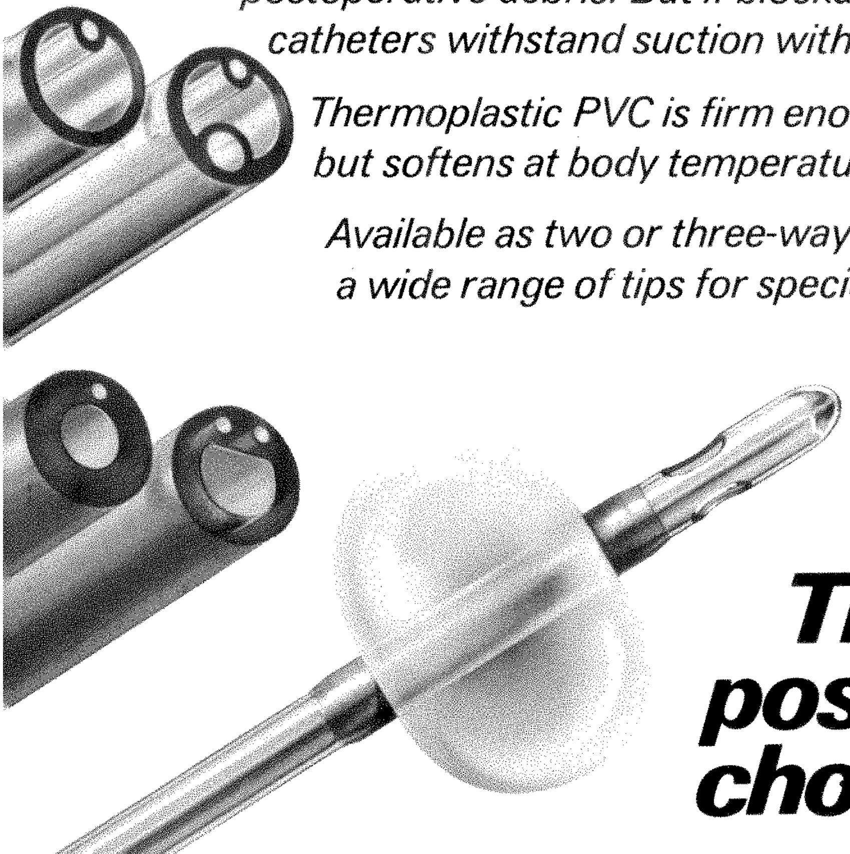

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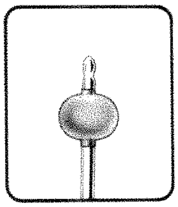

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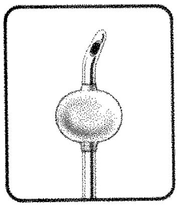

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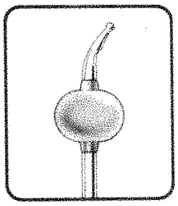

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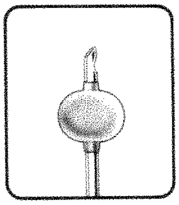

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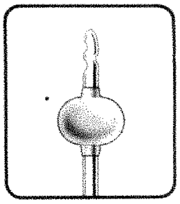

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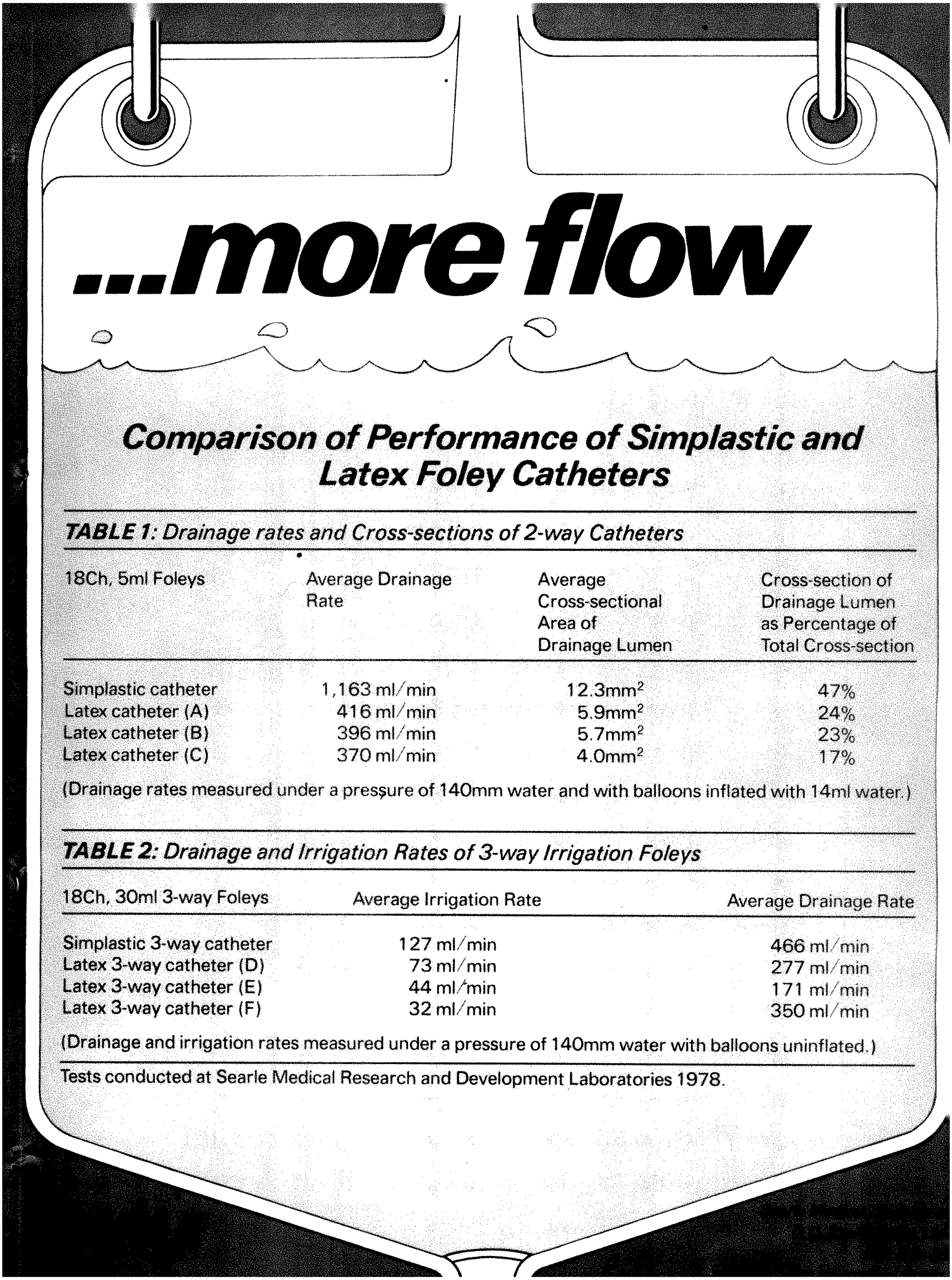

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TABLE 1: *Drainage rates and Cross-sections of 2-way Catheters*

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Latex catheter (B)	396 ml/min	5.7mm^2	23%
Latex catheter (C)	370 ml/min	4.0mm^2	17%

(Drainage rates measured under a pressure of 140mm water and with balloons inflated with 14ml water.)

TABLE 2: *Drainage and Irrigation Rates of 3-way Irrigation Foleys*

18Ch, 30ml 3-way Foleys	Average Irrigation Rate	Average Drainage Rate
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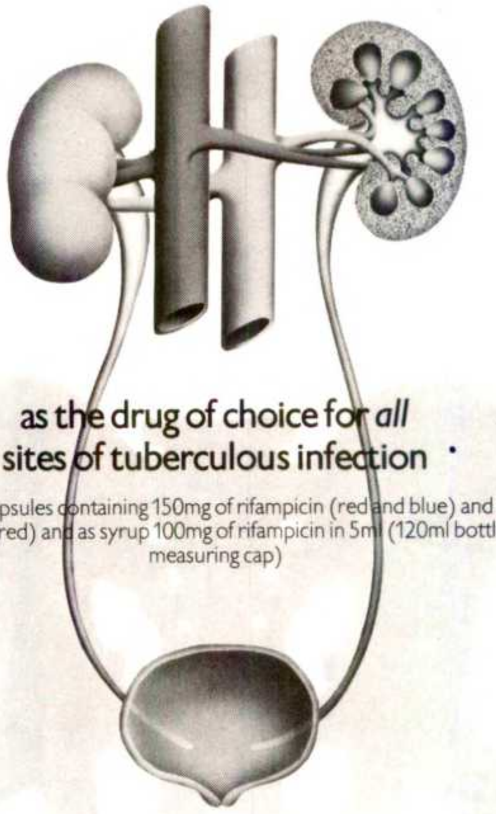

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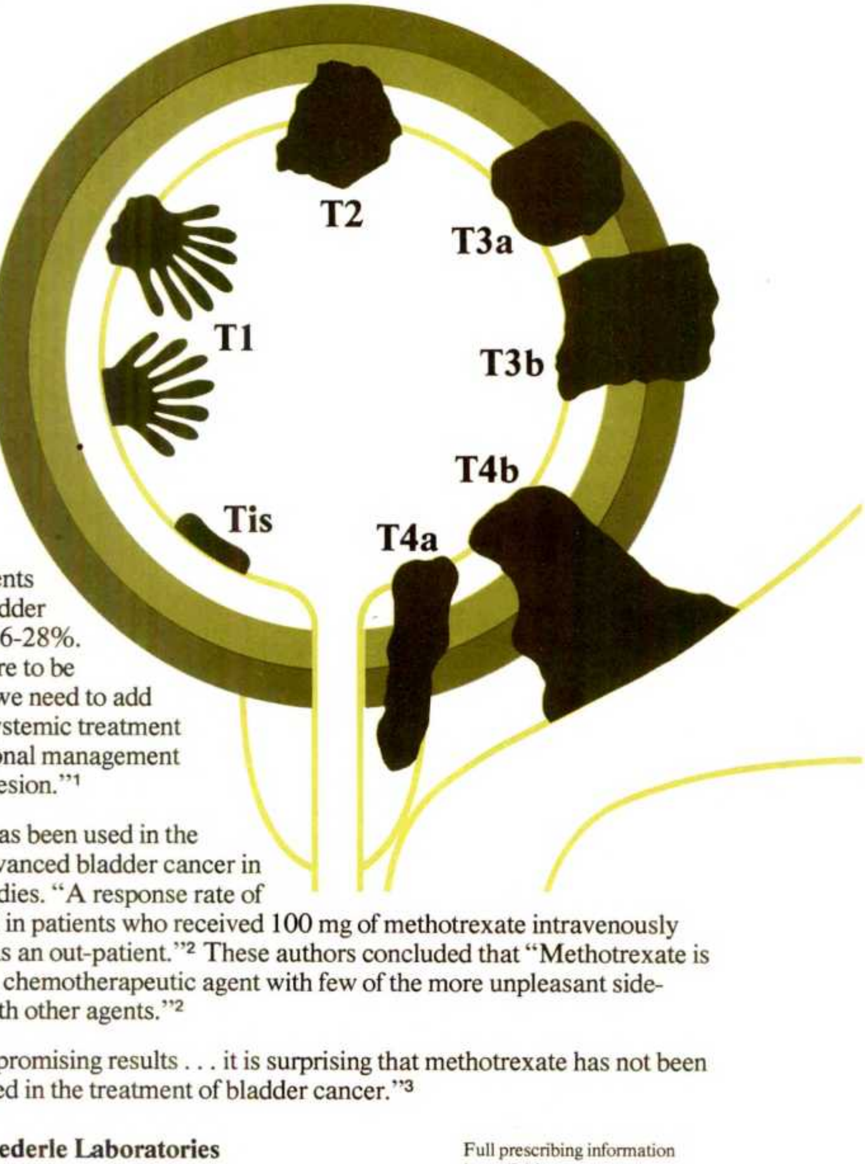

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1. *Brit. med. J.* 1977, 2, 1562
2. *Brit. J. Urol.* 1977, 49, 673
3. *Cancer Res.* 1977, 37, 2771

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Integrated Irradiation and Cystectomy for Bladder Cancer*

W. F. WHITMORE, JUN.

Urologic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, USA

Planned pre-operative irradiation and cystectomy for selected patients with bladder cancer was initiated approximately 20 years ago by a number of centres on the basis of the disappointing end results of treatment of bladder cancer by either irradiation or surgery and the empirical hope that the combination might lead to better results. This is a brief review of the logical basis for integrated treatment and of the Memorial Sloan-Kettering Cancer Center (MSKCC) experience with such therapy.

Logic of Integrated Treatment

The initial basis for integrated treatment was recognition that radiation therapy and surgery each controlled only limited numbers of bladder cancers (Whitmore, 1969), that combinations of irradiation and surgery resulted in apparently improved end results in certain instances (Barnes *et al.*, 1946; Emmett and Winterringer, 1955; Riches, 1960; Magri, 1962), and that a planned integration of these modalities might favourably affect end results. Over the past 10 years the accumulation of radiobiological evidence (Powers and Palmer, 1968; Perez, 1970) has provided a firmer basis for clinical studies of integrated treatment and includes: (1) demonstrations by clonigenic assay of tumour cells of an approximately exponential relation between radiation dose and surviving cell fraction such that relatively modest doses of irradiation are capable of inactivating the vast majority of a tumour cell population, the slope of the dose response curve being very steep up to the level of 90% cell inactivation; (2) demonstration that the sensitivity of a tumour cell population to conventional forms of irradiation is directly related to oxygenation, anoxic cells being relatively radioresistant; (3) demonstration that radiated tissues are less susceptible to the successful local implantation of tumour cells. Although the relevance of such experimental observations to the clinical situation has been appropriately questioned, clinical support for the validity of these concepts has been considerable (Cady, 1968a and b; Fletcher, 1973).

It is useful to examine hypothetically how, in the light of the above considerations, pre-operative irradiation might have a favourable influence upon the *basic causes* for bladder cancer treatment failure.

(1) *New primary tumour.* There is no acceptable evidence that radiation therapy diminishes the incidence of new tumour formation in the bladder, with the possible exception of the data of van der Werf-Messing (1978).

(2) *Incomplete resection of local extensions.* A favourable effect of pre-operative irradiation on incompletely resected local extensions might be anticipated from the potential sterilisation by such treatment of the well-oxygenated peripheral micro-extensions of tumour.

(3) *Iatrogenic local implantation or distant dissemination.* Pre-operative irradiation might be expected to have a salutary effect on iatrogenic local recurrences and distant metastases by a reduction in the viable tumour cell population and by the tumour bed effect.

(4) Pre-existing unrecognised metastases within the radiated volume, such as regional lymph node metastases, might be favourably affected by pre-operative irradiation, particularly if the metastases are microscopic in dimension (Fletcher, 1973). Pre-existing unrecognised metastases outside the radiated volume would be unaffected by pre-operative irradiation unless such an effect were mediated in some immunological way by the treatment of the primary tumour.

(5) Pre-existing recognised metastases inside or outside the radiated volume would probably not be benefited by a pre-operative radiation programme.

Patients and Results

Between 1949 and 1971 451 patients with bladder cancer had radical cystectomy, usually with bilateral pelvic lymph node dissection. All patients were subjected to a general evaluation including a complete history and physical examination, blood count, urine analysis, chest X-ray, intravenous urogram, serum electrolyte and liver profiles, and blood urea nitrogen and/or creatinine determinations. Liver scan, bone scan and radiographic skeletal survey were performed *only* for specific indications. Lymphography was not used at all.

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* This subject formed the basis of the Berk Pharmaceutical Lecture delivered at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Clinical staging of the bladder tumour *per se* was based upon the findings at cystoscopy, bimanual examination and appropriate biopsies under anaesthesia. Pathological staging was based upon the evaluation of the surgical specimen of radical cystectomy and bilateral pelvic lymph node dissection. The techniques of clinical and pathological staging remained the same throughout the period of this study. Discrepancies between the clinical and pathological stage have been discussed elsewhere (Whitmore *et al.*, 1977a).

Pelvic recurrences are defined as soft tissue recurrences within the pelvis with or without involvement of contiguous bone. Extrapelvic recurrences include all other evidence of recurrent bladder cancer. The technique of radical cystectomy with bilateral pelvic lymph node dissection cleanly exposes the bony and muscular walls of the pelvis and the major pelvic vessels but preserves the rectum (Whitmore, 1975).

For the purposes of analysis the 451 patients can be divided into 4 groups.

Group I included 137 patients treated by surgery alone in the interval 1949 to 1959.

Group II included 109 patients who had surgery following definitive megavoltage irradiation between 1949 and 1971. Such patients were referred for "salvage cystectomy" as radiation failures from 2 months to 8 years (average 1 year), usually following radiotherapy elsewhere. The latter usually consisted of 6000 rad to the bladder in 30 increments over 6 weeks by one of a variety of techniques. *These patients were derived from an unquantified total experience which must have included radiation successes, radiation failures who died, and the radiation failures referred for "salvage cystectomy". Whether the latter patients had persistent, recurrent or new lesions is largely undetermined.*

Group III included 119 patients who received a planned 4000 rad in 20 increments of 200 rad over 4 weeks through fields encompassing the true pelvis, and surgery 4 to 12 weeks (average 46 days) following irradiation in the interval 1959 to 1966.

Group IV included 86 patients who received 2000 rad in 5 increments of 400 rad each over a 1-week period to fields encompassing the bladder and true pelvis, followed by surgery within 2 weeks (average 2 days) in the period 1966 to 1971.

The validity of conclusions resulting from comparisons of these treatment groups has been legitimately questioned on the grounds that the 4 groups were more or less successively accumulated and did not constitute a controlled trial of 4 different approaches to bladder cancer management. On the other hand:

(*a*) Analysis of the 4 groups in relation to age, sex, tumour grade, tumour stage, tumour configuration (papillary versus solid), tumour multicentricity (solitary versus multiple), and prior surgical treatment reveals no significant differences to suggest a selection bias.

(*b*) The criteria of case selection and clinical staging have remained unchanged.

(*c*) There has been continuity of surgeons and radiation therapists in the conduct of the study.

(*d*) The radiation and surgical techniques used have undergone no relevant modifications.

(*e*) End results reported for the treatment of bladder cancers of different stages by various surgical or radiation techniques over the years encompassed by this study have been remarkably

Table 1 Five-Year Results

Status at 5 years	*Group I—137*	*Group II—109*	*Group III—119*	*Group IV—86*
Alive NED*	45 (33%)	43 (39%)	50 (42%)	36 (42%)
Dead with recurrence	66 (48%)	35 (32%)	47 (40%)	35 (41%)
Without recurrence†	25 (18%)	26 (24%)	22 (18%)	15 (17%)
Lost to follow-up	1 (1%)	5 (5%)	—	—

* NED = No evidence of disease. Later recurrence in 1 in Group I, 3 in Group II, 5 in Group III, and 1 in Group IV.

† Treatment complications in 19 in Group I, 22 in Group II, 13 in Group III, and 8 in Group IV.

Table 2 Five-year Survival According to Clinical Stage and Histological Grade

	Low clinical stage		*High clinical stage*	
	Low grade	*High grade*	*Low grade*	*High grade*
Group I	26/43 (60%)	9/23 (39%)	5/24 (21%)	4/46 (9%)
Group II	24/39 (62%)	2/8 (25%)	7/22 (32%)	10/35 (29%)
Group III	23/35 (66%)	11/23 (48%)	7/19 (37%)	10/42 (24%)
Group IV	12/20 (60%)	3/9 (33%)	12/29 (41%)	9/28 (32%)

Table 3 Five-year Survival According to *P*-T Relationship

	P<*T*	P≥*T*
Group I	2/6 (33%)	43/130 (33%)
Group II	27/46 (59%)	16/58 (28%)
Group III	27/48 (56%)	24/71 (34%)
Group IV	10/23 (43%)	26/63 (41%)

consistent (Whitmore and Batata, 1979), suggesting that the behaviour of bladder cancer has not materially altered over these years. More specifically, the 16% survival rate (10/64) in patients with T3 lesions treated by cystectomy alone in Group I in the interval 1949 to 1959 is similar to the 22% (16/70) reported by Prout *et al.* (1973) for similarly staged and treated patients.

(*f*) The indications for cystectomy have remained essentially the same over the years encompassed by this experience and are essentially (1) superficially infiltrating tumours, sufficiently multicentric in space or time to make conservative treatment impractical or impossible and (2) deeply infiltrating tumours unsuitable for segmental resection.

With regard to tumour grade, benign papilloma and 4 grades of bladder cancer are recognised. This series includes no papillomas. Low grade lesions include grade I and II tumours; high grade lesions include grade III and IV tumours. The vast majority of low grade tumours were graded II and the vast majority of high grade tumours were graded III.

The lesions categorised as low stage include T1S, T1 and T2 tumours and those categorised as high stage include T3 and T4 tumours. Amongst the low stage tumours the majority were T2 lesions (Group I, 42/66=63%, Group II, 37/47=78%, Group III, 36/58=62%, Group IV, 22/28=78%) and amongst the high stage tumours the majority were T3 lesions (Group I, 64/70=91%, Group II, 53/57=92%, Group III, 50/61=82%; Group IV, 52/57=91%).

Table 1 shows the 5-year results in the 4 groups. Four features are notable: (1) Survivals with no evidence of disease (NED) are marginally better in each of the radiated groups than in Group I. (2) Deaths from recurrence are marginally fewer in the radiated groups than in Group I. (3) Deaths due to causes other than cancer are virtually the same in all groups. (4) The overall impact of the combination of irradiation and surgery, when the groups as a whole are considered, is hardly impressive.

Table 2 is an analysis of 5-year survival according to clinical stage and histological grade for each of the 4 treatment groups. The specially selected nature of the patients subjected to "salvage cystectomy" (Group II) must be borne in mind. The following features are notable: (1) Stage for stage, patients with low grade tumours survive better than patients with high grade tumours in each of the groups, but the impact of grading on survival

Table 4 Five-year Survival According to *P*-T Relationship and Clinical Stage

	Low clinical stage		*High clinical stage*	
	P<*T*	P≥*T*	P<*T*	P≥*T*
Group I	—	35/66 (53%)	2/6 (33%)	8/64 (12%)
Group II	18/28 (64%)	8/19 (42%)	9/18 (50%)	8/39 (21%)
Group III	16/23 (70%)	18/34 (53%)	11/25 (44%)	6/37 (16%)
Group IV	3/8 (37%)	12/21 (57%)	7/15 (47%)	14/42 (33%)

Table 5 Pelvic Recurrence Alone in 5 or More Years According to Clinical Stage and Histological Grade

	Low clinical stage		*High clinical stage*	
	Low grade	*High grade*	*Low grade*	*High grade*
Group I	7/43 (16%)	5/23 (22%)	6/24 (25%)	20/46 (43%)
Group II	3/39 (8%)	0/8 (0%)	5/22 (23%)	7/35 (20%)
Group III	4/35 (11%)	3/23 (13%)	3/19 (16%)	9/42 (21%)
Group IV	2/20 (10%)	0/9 (0%)	4/29 (14%)	6/28 (21%)

Table 6 Pelvic Recurrence Only in 5 or More Years

Clinical stage	*Group I*	*Group II*	*Group III*	*Group IV*
T1S	0/7	0/1	0/9	0/1
T1	0/17	0/9	1/13	0/6
T2	12/42 (28%)	3/37 (8%)	6/36 (7%)	2/22 (9%)
T3	26/64 (40%)	9/53 (17%)	10/50 (20%)	8/52 (15%)
T4	0/6	3/4 (75%)	2/11 (18%)	2/5 (40%)

is apparently greater in the low stage than in the high stage tumours. (2) In patients with low stage tumours, whether of low or of high grade, no clear impact of prior irradiation on end results is apparent. (3) In patients with high stage tumours, whether of low or of high grade, prior irradiation is associated with improvement in 5-year survival rates.

Table 3 summarises 5-year survival rates for each of the groups in terms of apparent tumour downstaging. The latter was determined by comparing the pre-irradiation, pre-cystectomy clinical stage to the post-cystectomy pathological stage. Van der Werf-Messing (1973) pointed out that the beneficial effects of pre-operative irradiation are apparently limited to those patients whose tumours regressed (*P*<T) with such treatment. In Group I, downstaging is attributable to the clinical staging error, generally a small one in the case of clinical overstaging (6/136). In Group II, tumour downstaging is a consequence of clinical staging error and true radiation downstaging, bearing in mind the selection bias previously referred to and the clinical staging difficulties in the heavily irradiated pelvis. In Group III, tumour downstaging is a consequence of clinical staging error plus true radiation downstaging. In Group IV, downstaging is less (23/86=27%) than in Group III (48/109=44%). Assuming that the clinical staging error is the same in both groups, the logical explanation is that the lesser radiation dose and the shorter interval between radiation and surgery diminish the ***demonstrable*** tumour downstaging in Group IV patients. This explanation is consistent with the fact that the survival rates in the Group IV patients are essentially the same in the downstaged and the non-downstaged patients ***and*** that the survival rates in the non-downstaged patients are somewhat better than in the non-downstaged patients in any of the other groups. In any event, patients receiving irradiation whose tumours are detectably downstaged seem to have a survival advantage over patients not receiving irradiation or patients receiving irradiation whose tumours are not downstaged.

Table 7 Pelvic Recurrence Alone in 5 or More Years According to *P*-T Relationship

	P<*T*	P≥*T*
Group I	2/6 (33%)	36/130 (28%)
Group II	1/46 (2%)	13/58 (22%)
Group III	3/48 (6%)	16/71 (23%)
Group IV	1/23 (4%)	11/63 (17%)

Table 4 indicates the relationship between the 5-year survival rate and tumour downstaging relative to the clinical stage for each of the groups. Survival benefits from pre-operative irradiation are evident only in patients with high stage neoplasms. The difference in survival between downstaged and non-downstaged patients with high clinical stage lesions is less in Group IV than in Group III, probably due to the lesser incidence

Table 8 Extrapelvic Recurrence Alone in 5 Years or More According to Clinical Stage and Histological Grade

	Low clinical stage		*High clinical stage*	
	Low grade	*High grade*	*Low grade*	*High grade*
Group I	0/43 (0%)	3/23 (13%)	2/24 (8%)	8/46 (17%)
Group II	4/39 (10%)	4/8 (50%)	5/22 (23%)	4/35 (11%)
Group III	3/35 (9%)	6/23 (26%)	4/19 (21%)	10/42 (24%)
Group IV	5/20 (25%)	3/9 (33%)	6/29 (21%)	5/28 (18%)

Table 9 Pelvic Recurrence Alone From Time of Cystectomy

	Six months	*One year*	*Two years*	*≥ Five years*
Group I—136	16 (12%)	21 (15%)	29 (21%)	38 (28%)
Group II—104	7 (7%)	12 (12%)	13 (13%)	15 (14%)
Group III—119	12 (10%)	17 (14%)	17 (14%)	19 (16%)
Group IV—86	4 (5%)	7 (8%)	10 (12%)	12 (14%)

of *detectable* downstaging in the Group IV patients.

Table 5 indicates the frequency of pelvic recurrence alone for each of the treatment groups relative to tumour grade and stage. The incidence of pelvic recurrence only as a cause of treatment failure is less in Groups II, III and IV than in Group I for each of the grade and stage categories.

Table 6 shows a breakdown of pelvic recurrence rates for each of the treatment groups relative to each of the T categories. There were no pelvic recurrences with T1S lesions and only a single pelvic recurrence with a T1 lesion. Pelvic recurrences tend to increase progressively with T2, T3 and T4 lesions and are most dramatically reduced by prior irradiation in the T2 and T3 categories.

In Table 7 is given the incidence of pelvic recurrence alone for each of the treatment groups relative to whether or not tumour downstaging was evident. A conspicuous reduction in pelvic recurrence is noted in each of the irradiated groups in which demonstrable tumour downstaging occurred. Furthermore, in patients without demonstrable tumour downstaging, those in Group IV, wherein tumour downstaging is most difficult to detect, had the lowest incidence of pelvic recurrence.

Table 8 shows the incidence of extrapelvic recurrence only in the different groups relative to clinical stage and histological grade. The apparent paradox of an increased incidence of distant failure alone in each of the radiated groups compared to Group I is logically explicable on the basis of the reduction of pelvic recurrences in the radiated groups.

In Table 9 the incidence of pelvic recurrence alone is shown at various times after cystectomy for each of the groups. Except in Group I, the vast majority of pelvic recurrences were evident within 2 years following cystectomy.

In Table 10 is shown the incidence of extrapelvic recurrence with or without pelvic recurrence at various intervals after cystectomy for each of the groups. Although the majority of such recurrences are evident within 2 years of cystectomy, an appreciable number of such failures, especially in Groups II and III, become evident after 2 years.

Table 10 Pelvic and/or Extrapelvic Recurrence from Time of Cystectomy

	Six months	*One year*	*Two years*	*≥ Five years*
Group I—136	8 (6%)	17 (13%)	27 (20%)	29 (21%)
Group II—104	9 (9%)	13 (13%)	17 (16%)	23 (22%)
Group III—119	8 (7%)	16 (13%)	21 (18%)	34 (29%)
Group IV—86	8 (9%)	18 (21%)	21 (24%)	24 (28%)

Table 11 Factors Associated with Lymph Node Involvement

Cancer	*Group I—18*	*Group II—14*	*Group III—19*	*Group IV—16*
Solid	17	14	15	9
Solitary	17	12	14	9
T3-4*	17	11	12	10
G3-4†	13	9	15	11
Size >4 cm	12	12	10	11
Obstructive uropathy	13	9	15	11
Prior segmental or suprapubic resection	5	2	4	3

* High stage.
† Grade in 42/67.

Table 12 Incidence of Lymph Node Involvement According to Clinical (T) Stage

	T1	*T2*	*T3*	*T4*
Group I	1/17*	0/42	14/64 (22%)	3/6
Group II	0/9	3/37	8/53 (15%)	3/4
Group III	1/13†	6/36	7/50 (14%)	4/11
Group IV	0/16	6/22	9/52 (17%)	1/5
Total	2/55 (3%)	15/137 (11%)	38/219 (17%)	12/26 (46%)

Numerator = number with lymph node involvement.
Denominator = number of cases in category.
* Adenocarcinoma.
† Prior segmental resection.

In Table 11 are tabulated a number of factors which were associated with the presence of lymph node involvement in each of the groups. The correlations demonstrated are not surprising and are similar for all groups.

In Table 12 is demonstrated the incidence of lymph node involvement according to clinical stage for each of the treatment groups. The incidence of lymph node metastases increases with increasing T category. Although the incidence of lymph node involvement in the T3 categories in the radiated groups is less than in Group I, whether this indicates a salutary effect on regional lymph node metastases from prior irradiation or whether it is fortuitous is undetermined.

Table 13 shows the incidence of recurrence in the presence of lymph node involvement for each of the groups. A high proportion of patients with regional lymph node involvement apparently had only pelvic recurrence, possibly because such patients die from the disease before distant dissemination manifest itself or possibly because of an inherently regional pattern of tumour behaviour.

Five-year survival results in patients with lymph node metastases in the various groups are shown in Table 14. No benefit ascribable to pre-operative irradiation is evident.

In Table 15 is shown the hospital mortality in each of the 4 groups. Although hospital mortality was highest in the salvage cystectomy group, deaths from renal failure and sepsis were more or

Table 13 Incidence of Recurrence with Involved Lymph Nodes

Involved nodes	*Pelvic only*	*Extrapelvic only*	*Pelvic and extrapelvic*
Group I—18	8	4	5
Group II—14	6	3	—
Group III—19	7	3	6
Group IV—16	6	6	2
Total—67	27 (40%)	16 (24%)	13 (20%)

Table 14 Results at 5 Years with Involved Lymph Nodes

Involved nodes	*Alive without recurrence*	*Dead with recurrence*	*Dead of complications**	*Dead of other causes*
Group I—18	—	17	—	1
Group II—14	1	9	4	—
Group III—19	1	15	3	—
Group IV—16	1	14	1	—
Total—67	3 (5%)	55 (82%)	8 (12%)	1 (1%)

* Post-operative deaths.

less equally distributed among the 4 groups and it is difficult to implicate the use of irradiation as a conspicuous factor in mortality.

Discussion

Limitations in the MSKCC data resulting from the successive rather than randomised nature of the 4 clinical trials have been mentioned previously. The randomised clinical trials of Miller and Johnson (1973) and of Wallace and Bloom (1976) have demonstrated an advantage of pre-operative irradiation with cystectomy over irradiation alone. A number of uncontrolled studies (Van der Werf-Messing, 1973, 1975; Reid *et al.*, 1973, 1976) and the controlled study of Prout *et al.* (1973) have been reviewed elsewhere (Whitmore and Batata, 1979) and are in accord with the MSKCC experience in indicating better 5-year survival rates in patients with T3 lesions subjected to pre-operative irradiation with cystectomy than in those treated by cystectomy alone.

In evaluating MSKCC data it is useful to return to the causes of treatment failure and to examine the evidence that pre-operative irradiation has had a favourable impact upon them: (1) New primary tumour. The selection of cystectomy candidates as the subjects for investigation of the value of pre-operative irradiation was fortunate since there is little evidence that irradiation favourably alters the pattern of new tumour formation in the bladder and since bladder removal effectively eliminates this potentially confounding factor in evaluating the results of treatment. (2) Incomplete resection of local extensions and (3) Iatrogenic local implantation or distant dissemination. The data indicate that pre-operative irradiation reduces the incidence of pelvic recurrence. To what extent such pelvic recurrences are due to local micro-extensions transected during the course of conventional surgical removal and to what extent they are a consequence of iatrogenic local implantation from tumour spillage is undetermined. However, 2 additional considerations bolster the significance of this observation: (*a*) the salutary effects of pre-operative irradiation are most evident in the situations where the risk of local recurrence is the greatest. The minimal risk of pelvic recurrence in T1S and T1 tumours is indicated by the data in Table 6. In T2 and T3 tumours the pelvic recurrence rate is high and is apparently reduced by pre-operative irradiation. The data for T4 tumours is too sparse for interpretation. (*b*) Patients with radioresponsive tumours, *i.e.* those patients whose tumours are downstaged, achieve the greatest benefit from the integrated treatment. (4) Pre-existing unrecognised metastases. Whether or not pre-operative irradiation had a favourable influence upon regional lymph node metastases is uncertain. Radiation portal sizes (Whitmore *et al.*, 1977b) in the 2 pre-operative radiation regimes were not optimal, the radiation doses were less than those usually recommended (Fletcher, 1973), pathological study of the regional lymph nodes was done in routine fashion and the overall number of cases with demonstrated lymph node involvement was small (Tables 12, 13 and 14). The high incidence (40%) of pelvic recurrence only in patients with involved lymph nodes leaves open the possibility that improved methods of regional control may improve results in such patients.

Table 15 Mortality Under 5 Years From Causes Other Than Recurrence

	Hospital mortality	*Later complication or other cause*
Group I—137	19 (14%)	6 (4%)
Group II—109	17 (16%)	9 (8%)
Group III—119	13 (11%)	8 (7%)
Group IV—86	8 (9%)	7 (8%)

For patients with distant metastases, recognised or unrecognised, irradiation offers no expectation of benefit.

The 2 pre-operative radiation programmes utilised in the MSKCC experience produced equal effects on survival rates and on pelvic recurrence rates. The short course/low dose regime has physical, psychological and economic advantages for the patients (Whitmore and Batata, 1979). However, the short course regime lessens the opportunity for recognition of radiation response (tumour downstaging), a potentially important consideration in stratifying patients for alternative and/or adjunctive therapy. In any event, what constitutes optimal pre-operative irradiation has not been defined by this or any other study.

Development of techniques for predicting radiation responsiveness has long been a goal. Recognition of tumour downstaging as a gross morphological concomitant of a favourable response to irradiation is hardly a unique or surprising observation. MSKCC experience with the low dose/short course pre-operative radiation regime further emphasises the need for more sensitive and refined predictors in this regard. Ongoing investigations of a wide range of techniques—biochemical, cytological, immunological, electron microscopic, tissue culture, etc., as means of predicting the behaviour of bladders harbouring tumours may have application in assessing tumour radioresponsiveness as well. An analysis of such tumour features as histological grade, configuration (papillary or solid), number (solitary or multiple) or tumour diameter (<4 cm vs ≥ 4 cm in diameter) in each of the groups in the MSKCC experience has suggested that tumour size is the only one of such features which correlates with tumour radioresponsiveness.

It is concluded that:

1. Planned pre-operative irradiation improves the survival rates of patients with T3 tumours subjected to cystectomy.
2. The favourable effects of pre-operative irradiation are apparently restricted to those patients in whom radiation-induced downstaging ($P<T$) may be recognised and sensitive and reliable methods for predicting such radioresponsiveness are needed.
3. The beneficial effects of pre-operative irradiation seem largely attributable to a reduction in the incidence of pelvic recurrences.
4. The optimal regime of pre-operative irradiation remains to be defined. In the MSKCC experience either 4000 rad in 4 weeks or 2000 rad in one week seemed equally effective.

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Bacteriaemia and Bacteriogenic Shock in District Hospital Urological Practice

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Summary—The incidence of bacteriaemia and bacteriogenic shock was studied in 2 series of patients undergoing urological procedures. In the first series (A), 52 of 4333 urological patients had symptoms of bacteriogenic shock. Twenty-five of these had a positive blood culture, giving an incidence of shock with proven bacteriaemia of 0.58%.

In the second series (B) 628 patients had blood cultures taken after urological procedures with an incidence of bacteriaemia of 12.7%. Bacteriaemia is most common after prostatic surgery (transurethral prostatectomy 27%, retropubic prostatectomy 37%, prostatic biopsy 20%), and is usually due to *Esch. coli, Proteus* species and *Ps. aeruginosa*. In hospital practice these organisms are unlikely to be sensitive to common antibiotics and initial therapy with an aminoglycoside is justified, while awaiting the results of blood culture.

A parallel study was made in 2 district hospitals (A and B) to determine the incidence of symptomatic and asymptomatic bacteriaemia resulting from urological procedures. The same medical staff, surgical techniques and bacteriological facilities were employed in both hospitals. At "A" a record was kept of all patients clinically suspected of having bacteriogenic shock, irrespective of blood culture findings, and at "B" a large series of patients undergoing urological procedures had routine blood cultures performed in a prospective study of the incidence of bacteriaemia.

Patients and Methods

Series A

Fifty-two patients with clinically suspected bacteriogenic shock after urological procedures were studied during the period April 1972 to April 1976. The criteria for inclusion were pyrexia, rigors and a fall in blood pressure associated with clinical features of shock. Blood cultures were taken at the time of diagnosis and on the following 2 days. Routine treatment was intravenous fluid, an antibiotic (usually gentamicin or tobramycin), and large doses (300 mg) of hydrocortisone.

Series B

Six hundred and twenty-eight patients, consisting of day-cases and in-patients, were studied between October 1974 and December 1975. Blood cultures were taken 3 h after urological procedures in all patients, and from in-patients on the following 2 days. Approximately one-third of the patients also had blood cultures taken 5 min after instrumentation and this was preceded by the taking of a skin swab at the site of venepuncture.

Blood Culture

Five millilitres of blood were collected from the patient's antecubital fossa, the skin having first been prepared with 70% isopropyl alcohol and allowed to dry. The sample was added to a blood culture bottle containing 50 ml glucose broth (Southern Group Laboratories) with para-aminobenzoic acid, penicillinase and liquoid. This was incubated at 37°C and after 2, 7 and 14 days subcultured on to blood agar, MacConkey agar and heated blood agar plates. The blood agar and MacConkey agar plates were incubated at 37°C for 18 h and the heated blood agar plates were incubated at 37°C in 10% carbon dioxide for 18 h. Anaerobic subcultures were not performed at this stage. A Gram-stained smear was made from the blood culture when it was subcultured on the second day; if bacteria were present in the smear, blood cultures were subcultured

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Table 1 Series A—Surgical Procedures Associated with Bacteriaemia

Transurethral resection prostate	16*
Transurethral resection bladder tumour	1
Retropubic prostatectomy	10*
Transvesical prostatectomy	1
Cystoscopy	3
Bladder biopsy	2
Prostatic biopsy	8
Ureterolithotomy	1
Insertion of catheter	4
Removal of catheter	6

* 1 case after removal of catheter.

anaerobically on blood agar at 37°C in 90% hydrogen and 10% carbon dioxide for 48 h in a McIntosh and Filde's jar.

Organisms were identified by examination of a Gram-stained film of the culture. *Staph. aureus* was distinguished from *Staph. albus* by the coagulase test. Gram-negative bacilli were identified by the A.P.I. 20 E system (Cellmark). Corynebacteria are Gram-positive rods arranged in palisades, and those which failed to ferment sugars were classified as "diphtheroids". Streptococci were identified by standard techniques (Cruickshank *et al.*, 1975). Antibiotic sensitivity testing was also performed by the method of Stokes (1975).

Results

Series A

In 25 of the 52 patients one or more blood cultures were positive. In the remaining 27 all 3 cultures were negative. The surgical procedures performed are listed in Table 1. *Esch. coli* and *Proteus* species were the most commonly cultured organisms (Tables 2 and 3). Before the results of cultures were known 22 patients were treated with gentamicin and 18 with tobramycin. Four patients had ampicillin, one cotrimoxazole, one streptomycin with penicillin and 6 had no treatment. Thirteen patients in this series had previously infected urine before bacteriogenic shock was suspected, but at the time shock developed all were on an appropriate antibiotic. Six of those with infected urine had positive blood cultures and 7 had negative cultures.

Table 2 Series B—Causes of Bacteriaemia

Organisms	*Cases*
Esch. coli	14
Proteus species	5
Staph. aureus	2
Staph. albus	1
Cl. perfringens (Cl. welchii)	1
Ps. aeruginosa	1
Str. faecalis	1

Of the 52 patients, 48 recovered and 4 died (2 with *Esch. coli* bacteriaemia and 2 with *Proteus spp.* bacteriaemia). One patient, aged 89, died of bacteriogenic shock alone and in the remaining 3 patients the cause of death was confirmed at post mortem as bacteriaemia and bronchopneumonia, bacteriaemia and myocardial infarction, and bacteriaemia and pulmonary embolism. These patients were aged 71, 64 and 75 years respectively.

During the period of this study 4333 patients had urological procedures at "A". This gives an overall incidence of patients with symptoms suggestive of bacteriogenic shock of 1.2%. Twenty-five had a positive blood culture, giving an incidence of shock with proven bacteriaemia of 0.58%.

Series B

All of the 628 patients had blood cultures taken 3 h after urological procedures and 216 also had cultures taken at 5 min. The overall incidence of bacteriaemia in this series was 12.7%. Of these 3.7% were symptomatic and 9% asymptomatic. The patients with symptoms had 2 of the 3 criteria of bacteriogenic shock (pyrexia, rigors and a fall in blood pressure), which could not be attributed to other causes. Three per cent of the patients studied had these symptoms without a positive blood culture.

The incidence of bacteriaemia and symptoms after different urological procedures is given in Table 4. Table 5 lists the bacteria cultures in both symptomatic and asymptomatic cases and Table 6 indicates on which day the blood cultures were first positive in 23 patients with symptoms. Table 7 gives the positive blood cultures and bacteria cultured in patients who had 5-min and 3-h cultures. None of these was symptomatic. In addition, of 216 patients having a 5-min culture performed, 142 had skin swabs taken at the site of venepuncture and 74 of these had positive swabs for *Staph. albus* and 4 for *Staph. aureus*. There was no relationship between these results and subsequent blood cultures. Sixty-four patients had sterile swabs.

There were no deaths from bacteriogenic

Table 3 Series A—Antibiotic Sensitivities

	Escherichia coli *(14 cases)*			Proteus *species (5 cases,*		
	Resistant	*Sensitive*	*Not tested*	*Resistant*	*Sensitive*	*Not tested*
Tetracycline	5	9	0	4	1	0
Ampicillin	7	7	0	4	1	0
Cotrimoxazole	1	13	0	1	4	0
Cephaloridine	3	11	0	1	4	0
Gentamicin	0	11	3	0	5	0
Tobramycin	0	9	5	0	3	2

Table 4 Series B—Incidence of Bacteriaemia

		Bacteriaemia with symptoms	*Bacteriaemia without symptoms*	*Symptoms without bacteriaemia*
Cystoscopy	400	2 (0.5%)	35 (8.8%)	3 (0.75%)
Cystoscopy + bladder biopsy	33	2 (6%)	2 (6%)	2 (6%)
Dilatation	86	3 (1.3%)	12 (13.9%)	1 (1.3%)
Prostatic biopsy	15	0	3 (20%)	1 (6.6%)
Transurethral resection	56	10 (17.8%)	5 (8.9%)	7 (12.3%)
Retropubic prostatectomy	22	8 (36.8%)	0	5 (22.8%)
Ureteric surgery	9	0	0	0
Urethroplasty	5	0	0	0
Renal surgery	3	0	0	0
Testicular surgery	3	0	0	0

Table 5 Series B—Organisms in symptomatic and asymptomatic cases

	Cystoscopy		*Cystoscopy and bladder biopsy*		*Dilatation*		*Prostatic biopsy*		*Transurethral resection*		*Retropubic prostatectomy*	
	S	*A*	*S*	*A*	*S*	*A*	*S*	*A*	*S*	*A*	*S*	*A*
Esch. coli	0	0	1	1	0	1	0	1	5	1	2	0
Proteus species	0	0	0	0	0	0	0	0	1	0	2	0
Staph. aureus	0	1	0	0	0	1	0	1	0	1	0	0
Staph. albus	1	25	0	1	1	4	0	1	3	2	0	0
Ps. aeruginosa	0	0	0	0	0	0	0	0	1	0	2	0
Str. faecalis	1	1	0	0	0	1	0	0	0	0	1	0
Str. viridans	0	1	1	0	0	0	0	0	0	0	1	0
Aerobic spore bearers	0	7	0	0	0	4	0	0	0	1	0	0
Diphtheroids	0	0	0	0	0	1	0	0	0	0	0	0

(S = Symptomatic) (A = Asymptomatic)

shock during this study. The age of the patients ranged from 27 to 89 years with a peak incidence of bacteriaemia in the eighth decade. In this series bacteriaemia with symptoms has not been recorded below the age of 50 years.

Discussion

Bacteriaemia is common in urological patients and, if uncontrolled, carries a high mortality (Weil *et al.*, 1964; Winslow *et al.*, 1973). Bacteriogenic shock in urological patients may be due to both Gram-positive and Gram-negative organisms (Sullivan *et al.*, 1973; Winslow *et al.*, 1973). During 1972, the year that routine reporting by laboratories of significant positive blood cultures began, 2672 patients with bacteriaemia were reported in the United Kingdom and Republic of Ireland and of these 13% died. The greatest mortality was in patients over the age of 65 years (*British Medical Journal*, 1975).

Table 6 Series B—Day on Which Culture was Positive

Twenty-three patients with symptoms	
First day	19
Second day	3
Third day	1

Our studies were initiated to answer several questions. Firstly, we wished to know the incidence of bacteriaemia in the urological unit and to establish how often this could be diagnosed on clinical features. Secondly, we wished to determine how many blood cultures were necessary to make the diagnosis, the causative organisms and their antibiotic sensitivity. Thirdly, were we justified in using the aminoglycosides gentamicin and tobramycin to initiate treatment while awaiting blood culture results, as both of these antibiotics are toxic to the eighth cranial nerve, and tobramycin may diminish renal function? Finally, by being aware of the incidence can we reduce the mortality?

In Series A a diagnosis of bacteriaemia was confirmed by culture in just under half of the patients clinically suspected of having the condition. Four of the 25 patients with bacteriaemia and clinical symptoms died in this series (19%). Of the 4 who died 3 were not initially treated with the correct antibiotic, although they were all given aminoglycosides before death. These patients were all elderly and had had prostatic surgery.

There were no deaths in Series B. This was probably because both the medical and nursing staff were alerted to the possibility of bacteriaemia by the blood cultures which were done as part of the standard management of these patients.

Escherichia coli and *Proteus spp.* were the most commonly cultured organisms in Series A. They were usually resistant to ampicillin, tetracycline and cephaloridine. Most organisms were sensitive to cotrimoxazole, but this drug was not available in parenteral form at the beginning of this study.

Table 7 Series B

Bacteria	*5 min*	*3 h*	*Both*
Staph. albus	12	5	1
Aerobic spore bearers	1	6	0
Str. faecalis	2	1	0
Esch. coli	2	0	0
Diphtheroids*	1	0	0

Thus we felt justified in using gentamicin and tobramycin as our initial therapy. In both series, however, Gram-positive cocci may sometimes be associated with symptoms.

Both our series indicated that prostatic surgery gave the highest incidence of both symptomatic and asymptomatic bacteriaemia (transurethral prostatectomy 27%, retropubic prostatectomy 37%, prostatic biopsy 20%). This agrees with the findings of Sullivan *et al.* (1973), who found an incidence of 31% following transurethral resection in patients with sterile urine and 52% in patients with infected urine at the time of operation. Age and the length of time patients undergoing prostatic surgery have pre-operative and post-operative catheters may also be factors. Series A showed that the onset of symptoms may be associated with the removal of the catheter. Urethral dilatation also caused a high incidence of bacteriaemia (15%). Following these procedures. *Esch. coli, Proteus spp.*, and *Ps. aeruginosa* were the common organisms cultured. We observed with interest that although 52 urethroplasties were performed in Series B, this procedure was not associated with bacteriaemia. This supports the hypothesis that infection most frequently follows prostatic manipulation rather than urethral trauma, and agrees with the observations of Bjorn *et al.* (1950) and Slade (1958).

The incidence of positive blood cultures following cystoscopy was much lower; staphylococci, especially *Staph. albus*, were sometimes encountered. *Staph. albus* was commonly isolated from the blood 5 min after instrumentation, but not in samples taken 3 h later. There appeared, in our study, to be no relationship between its presence in the blood and its culture from skin swabs taken at the site of venepuncture. Sometimes the organism was also present in later cultures, when it was occasionally associated with symptoms. Raine *et al.* (1975) observed that *Staph. albus* and *Staph. aureus* may cause fever after oesophageal bouginage. They also observed that the source was not to be found in the throat or pharynx, but on the instruments used for dilatation.

Bacteriaemia was usually evident in the first blood culture, but occasionally bacterial diagnosis was not made until a second or third culture on subsequent days was taken. Therefore at least 3 successive daily blood cultures should be taken.

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Rupture of the Urinary Bladder in Children. The Importance of the Double Lesion

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Summary—We report 10 cases of rupture of the urinary bladder in children. Only one patient was a girl. The rupture was caused by a road accident in 6 cases and occurred "spontaneously" in 4.

Rupture of the bladder may be difficult to diagnose. In many patients the vesical rupture is not the only abnormality in the urinary tract and a thorough investigation is necessary.

The majority of the bladder ruptures in these children were intraperitoneal, which contrasts with the reported experience in adults.

Injuries of the lower urinary tract are uncommon during childhood and rupture of the urinary bladder is rare in children despite the fact that the bladder is an abdominal organ in infancy. During the last 27 years only 10 children with rupture of the bladder have been seen at this hospital.

Case Reports

Case 1. A boy of 4 years was admitted after having been knocked down by a motor car in 1951. There was bruising in the right groin and lower abdomen and a fracture of the left superior pubic ramus. A catheter was passed with ease into the urethra but no urine was obtained. At laparotomy the dome of the bladder was found to be ruptured into the peritoneal cavity. The rent was sutured and a suprapubic catheter inserted. The catheter was removed after 7 days and the boy made an uneventful recovery.

Case 2. In 1957 a girl of 3 years was admitted after being knocked down by a van. She was shocked and in severe pain. There was profuse bleeding from the perineum. There were multiple fractures of the pelvis and right femur. Air was present in the soft tissues of the pelvis and an enormous haematoma developed in the right iliac fossa and flank. Under anaesthesia a catheter was passed into the bladder and, to control the haemorrhage, a pack was put into the vagina. There was intermittent haematuria and during the eighteenth week in hospital an IVP failed to demonstrate function in the right kidney. At right nephrectomy a devascularised kidney, only 4 cm long, was found. Over a period of 3 years the child gradually recovered and regained normal urinary continence.

Case 3. A shocked, unconscious boy aged 3 years was admitted in 1964. He had been knocked down by a lorry and the wheels had passed over his abdomen. There was a fracture of the pelvis and blood issued from his urethra. The child died on the way to the operating theatre. Post mortem examination revealed a large retroperitoneal haematoma and both sides of the diaphragm were ruptured. The kidneys lay within the thoracic cavities. There was an extraperitoneal rupture of the anterior wall of the bladder.

Case 4. In 1966 an 8-year-old boy was knocked down by a motor car. He was shocked and semiconscious, and on the right side there was a laceration of the scalp and fractures of the clavicle, humerus, tibia and fibula. Both pubic rami were fractured. An intravenous pyelogram was normal, without extravasation, but the boy passed no urine. A catheter was passed via the urethra and over 500 ml of blood-stained urine was obtained. A cystogram demonstrated a "tear drop bladder" with extravasation of contrast at the junction of the bladder and prostate (Fig. 1). The urethral catheter was retained and on the eleventh day a cystogram was normal. The catheter was removed on the twenty-seventh day and the boy made an uneventful recovery, without stricture formation.

Case 5. A shocked 10-year-old boy was admitted to another hospital in 1972. He had been struck by a car, causing fractures of the left frontal bone and ischium and of both femora, tibiae, and pubic rami. An intravenous pyelogram was normal. At laparotomy he was found to have a torn omentum, a ruptured spleen and an intraperitoneal rupture of the bladder. There was

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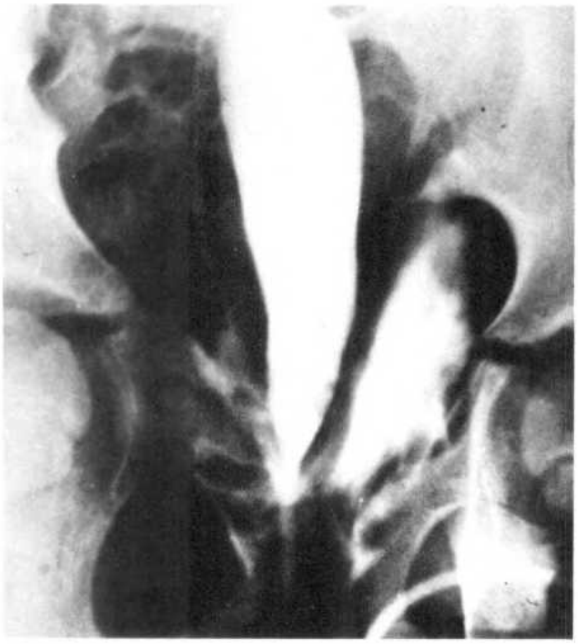

Fig. 1 Cystogram of Case 4 demonstrating a "tear drop bladder" and extravasation of contrast material into the extraperitoneal tissues of the pelvis.

also a partial rupture of the prostatic urethra. The bladder was sutured and suprapubic and urethral catheters inserted. After the catheters were removed on the ninth day, urine leaked suprapubically and the boy became uraemic. He was transferred to this hospital on the nineteenth day. The bladder was enlarged, and a suprapubic catheter was therefore inserted as well as a urethral splint. These were retained until the sixty-fourth day following the accident. Since discharge the boy has failed to reattend.

Case 6. In 1977 a boy aged 3 years was knocked down by a car. On admission he had muscle guarding in the lower abdomen but was not shocked. There was a fracture of the left superior pubic ramus. An intravenous pyelogram was normal. At laparotomy the only injury was a tear in the fundus of the bladder. This was closed in 2 layers with catgut sutures and the bladder drained by a Foley urethral catheter only. This catheter was removed on the ninth day but by the next day urine had collected in the extravesical tissues around the bladder base and prostate. The urethral catheter was reinserted. On the sixteenth day a cystourethrogram was normal. The catheter was then removed and the boy made a full recovery.

Case 7. A neonate aged 6 hours was admitted with a distended abdomen in 1956. Radiographs suggested that there was ascites. At laparotomy a grossly hypertrophied bladder was found to have ruptured on the posterior aspect. The edge of the defect was biopsied and the wall then closed in 2 layers. A suprapubic catheter was inserted. Subsequently a cystourethrogram demonstrated urethral valves and the biopsy was reported to consist of normal vesical components. The valves were destroyed. At the age of 2 years an intravenous pyelogram was normal and he was fully continent of urine.

Case 8. In 1965 a neonate had an open thoracolumbar myelomeningocele repaired. The bladder became distended and was difficult to express. On the eighth day she became anuric and the abdomen was distended. A cystogram confirmed the diagnosis of vesical rupture; the rupture was thought to be intraperitoneal but at operation an extraperitoneal rupture was discovered on the right anterolateral aspect of the bladder. This was closed in 2 layers with catgut and a suprapubic catheter inserted. On the eleventh day the repaired myelomeningocele broke down and the infant died from septicaemia on the nineteenth day.

Case 9. A boy aged 3 months was admitted with fever, convulsions, diarrhoea and vomiting in 1969. The abdomen was distended and there was an erythematous swelling in the inguinal region. As a neonate he had had an open myelomeningocele repaired. Following admission he suffered a cardiac arrest. Because of his symptoms and signs he was thought to have bacteriaemic shock complicating a strangulated hernia. After resuscitation he underwent surgery and the inguinal swelling was found to be due to extravasated urine. The abdominal distension was due to urinary ascites and there was an intraperitoneal rupture of a vesical diverticulum. This was repaired but the infant died on the twenty-fifth post-operative day.

Case 10. A mentally retarded boy with cerebral palsy was admitted in 1977. He was nearly 3 years old and was known to have suffered from recurrent urinary infections. An intravenous pyelogram had demonstrated chronic pyelonephritis on the right side. For some months the child had been unable to pass urine and the father had been taught to "express" the boy's urine. Early on the day of admission the boy had slipped from the father's knee and later the child had started to vomit. No urine could be expressed. Because of the mental condition of the boy examination was difficult but there seemed to be tenderness in the hypogastrium and the abdomen was distended. A catheter was passed into the urethra and clear urine was obtained. The catheter was removed and the boy became anuric. Urinary ascites was diagnosed and a cystogram revealed a filling defect in the dome of the bladder, thought to be haematoma, and contrast passed into the peritoneal cavity (Figs. 2, 3 and 4). Laparotomy confirmed that the bladder was ruptured, but the defect had a thickened edge suggesting a perforation of some standing (Fig. 5). Otherwise the bladder seemed to be normal. A biopsy was taken from the edge of the tear and the bladder

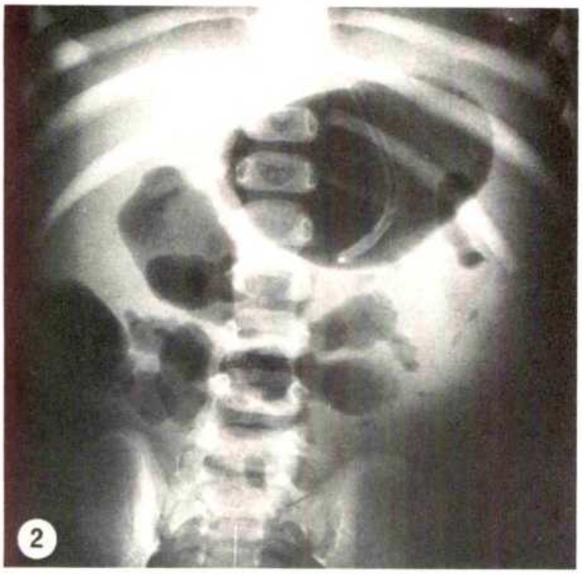

Fig. 2 Supine film of Case 10 demonstrating urinary ascites. There were no fluid levels on the erect film.

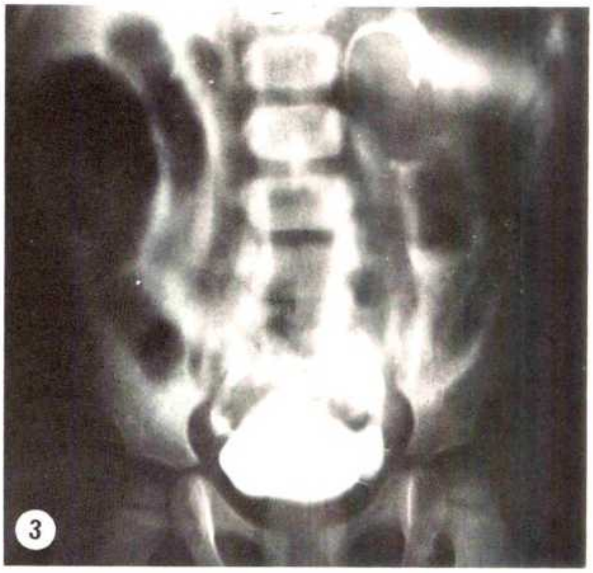

Fig. 3 IVP film of Case 10 taken 15 min after the injection of contrast. Note the irregularity of the fundus of the bladder and the passage of the contrast material into the peritoneal cavity.

repaired. A suprapubic catheter was inserted. The biopsy was reported as an embryonic sarcoma (Fig. 6). Subsequently the upper half of the bladder was excised. Although it was normal to the naked eye, microscopic examination demonstrated that there was tumour to the limit of the resection. In view of recent encouraging reports of good results without mutilating surgery and the general condition of the child it was decided to continue treatment by radiotherapy alone. One year later there was no evidence of metastases.

Discussion

Of the 134,687 patients admitted to this hospital between 1968 and 1977, 45,878 were surgical cases. Ninety-two of these were children suffering from urinary tract trauma, grouped as follows: renal injury 73, ureteric damage 1, complete division of the urethra 3, partial rupture of the urethra 11, rupture of the bladder 3, rupture of the bladder and partial rupture of the urethra 1. Rupture of the urinary bladder is rare during childhood and accounts for less than 5% of the cases of urinary tract trauma in this series. A similar incidence has been recorded by Mertz *et al.* (1963). Urethral injuries occurred in 16% of cases in this series; this incidence is higher than that reported by other authors but could be accounted for by the special referral of some of these cases to the urologist at this hospital (Hagberg *et al.*, 1977).

Of our 10 cases of rupture of the urinary bladder, 6 were caused by road accidents, and in all of these there was at least one fracture of the pelvis, the pubic region being damaged in all

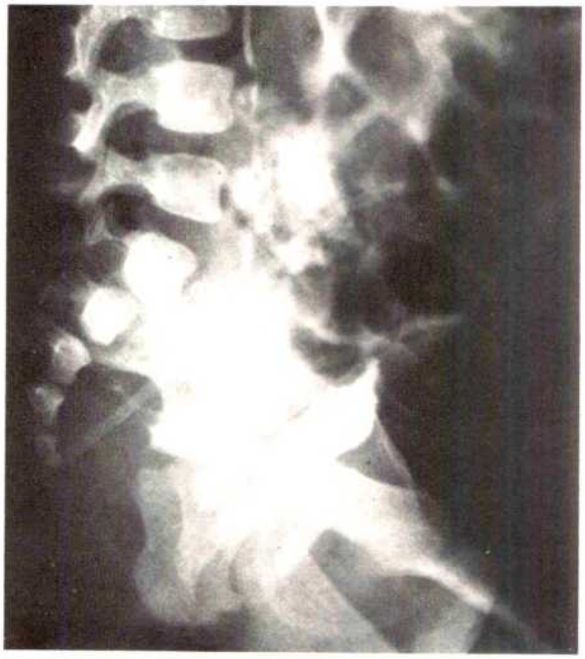

Fig. 4 Lateral film of the cystourethrogram of Case 10 demonstrating contrast material in the rectovesical pouch posterior to the small bladder.

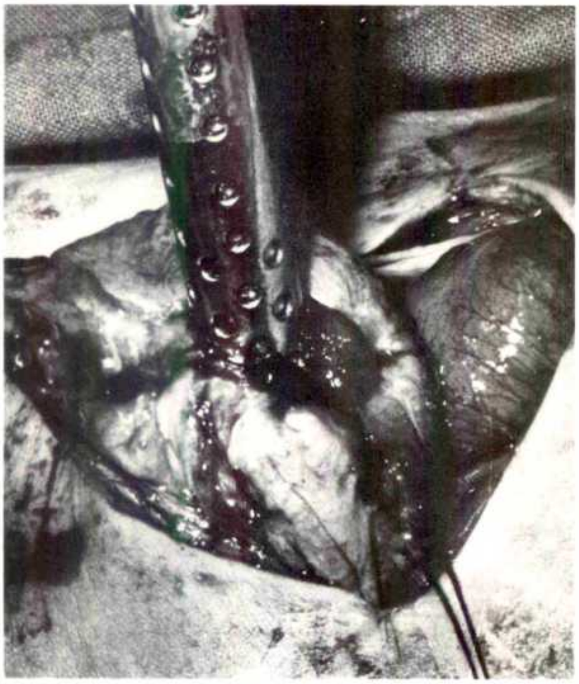

Fig. 5 Operative photograph of Case 10 demonstrating the suction tube passing through the tear in the bladder wall. Note the thickened edge of the defect (to the right of the sucker in the photograph).

(Wakeley, 1929; Johnston, 1968; Prather, 1970; Hagberg *et al.*, 1977). Rupture of the bladder or urethra occurs in 1 to 25% of cases of fracture of the pelvis in adults (Wakeley, 1929; McCague and Semans, 1944; Prather and Kaiser, 1950; Richardson, 1951, Mitchell, 1968; Prather, 1970) and is extraperitoneal in nearly 80% of cases. In this series of children, more than half of the ruptures were intraperitoneal (Koskela *et al.*, 1977). Urethral and vesical injuries are rare in girls and the vagina is usually involved, as in Case 2 (Johnston, 1968; Prather, 1970; Koskela *et al.*, 1977).

Four of the road accident cases sustained severe, multiple injuries and were shocked. In the absence of multiple injuries, shock is not a feature of rupture of the bladder (Rieser and Nicholas, 1963). However, marked muscle guarding was present in the lower abdomen in at least 2 of the cases without severe trauma, but would have been difficult to assess in the infants with myelomeningocele, one baby being brought to hospital several days after the illness had begun and the other being in the early post-operative period (Campbell, 1929).

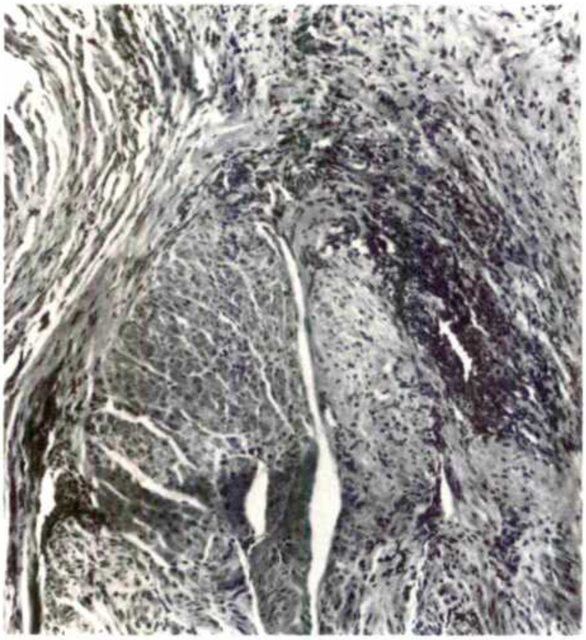

Fig. 6 Biopsy of the edge of the vesical perforation demonstrating massive infiltration by small malignant cells (H & E ×50).

In retrospect, several of these cases were inadequately investigated. In Case 2 the child was severely ill but the persistent haematuria should have led to the detection of the devascularised kidney at an earlier stage. In Case 6 the extraperitoneal part of the bladder should have been inspected at the time of surgery, or the bladder should have been opened to allow inspection of the wall from within (Prather and Kaiser, 1950), or the cystogram should have been performed much sooner. In this case it is difficult to explain the collection of urine about the bladder base on the tenth day, except by postulating that in addition to the sutured intraperitoneal laceration there had been an undiagnosed extraperitoneal tear of the bladder or an incomplete rupture of the urethra. Such tears are said to occur mainly in the anterolateral bladder wall close to the bladder neck, as in Case 4. That such double ruptures have been recorded is not surprising, but the combined intraperitoneal and extraperitoneal tears of the bladder are said to occur mainly in cases of penetrating injury. Mitchell (1968) has stressed that in cases of lower urinary tract trauma in adults, 10% have rupture of both bladder and urethra. The aetiological importance of a full bladder at the time of injury had been emphasised in these cases. It is abundantly clear that any case of lower urinary tract trauma requires thorough investigation of the whole urinary tract; otherwise any second site of damage will be missed and the child may later present with loss of renal function or with urethral stricture (Rexford, 1939; Mitchell, 1968; Hagberg *et al.*, 1977; Koskela *et al.*, 1977). This is particularly the case when a catheter has been inserted as part of the management of the seriously injured child, and in the case of the intraperitoneal rupture of the bladder when the rent may be temporarily occluded by a coil of intestine or a plug of omentum (Kamat *et al.*, 1970; Prather, 1970).

The so-called "diagnostic catheter" is so frequently misleading as to be condemned as totally without value, as is demonstrated in Case 10 where the catheter, in fact, drained the urinary ascites (Mitchell, 1971). Furthermore, the catheter may cause damage to the urethra (Mitchell, 1968). Cystoscopy may reveal a tear in the bladder wall, but it is valueless if the bladder leaks so much that it cannot be distended or if the instrument passes into coils of intestine (Rexford, 1939). Prather and Kaiser (1950) and Prather (1970) discouraged any attempt at cystoscopy. Rieser and Nicholas (1963) were probably wise in recommending cystoscopic examination in those cases suspected on clinical grounds but in which the cystograms were normal. Although cystourethrography sometimes gives false negative results (Stone, 1931; Mitchell, 1971), it is the most accurate methods of diagnosis provided that the contrast material has a viscosity similar to that of water (Prather and Kaiser, 1950; Rieser and Nicholas, 1963; Prather, 1970). We do not recommend the use of air as a contrast medium because air embolism may occur. At present we use "Urografin 150"* as the contrast material.

For intraperitoneal ruptures surgery is mandatory; otherwise the mortality rate is high (Koskela *et al.*, 1977). However, the operation need not be undertaken as an emergency and up to 24 hours can be spent in resuscitation and detailed investigation prior to surgery. After 24 hours the mortality rate rises sharply. In a child we recommend closure of the tear in one layer using interrupted chromic catgut sutures as advocated by Johnston (1968). Two-layer closure is not necessary and may cause ischaemia of the suture line with delayed healing. Drainage of urine from the peritoneal cavity is strongly recommended (McCague and Semans, 1944). Efficient bladder drainage is as important as suture of the rent (Bliss *et al.*, 1964). In cases of extraperitoneal rupture the tear may be difficult to find and surgical repair may not be necessary, although extravasated urine must be adequately drained (Stone, 1931). Good results have been achieved by simple bladder drainage, as in Case 2, where it would have been difficult to find the bladder amongst the bone fragments and massive haematoma. However, in most cases suprapubic cystostomy is advocated in preference or in addition to urethral drainage alone. From a study of Cases 5 and 6 it seems that more than 10 days of bladder drainage are usually required in this type of injury, although Case 1 appears to be an exception to this rule.

"Spontaneous" rupture of the bladder, or rupture in the absence of pelvic fracture or instrumentation, means that the bladder is abnormal (Stone, 1931; Thompson *et al.*, 1965). True spontaneous rupture is rare but may be a recurring problem (Bunton, 1952; Bliss *et al.*, 1964; Kamat *et al.*, 1970). Spontaneous bladder rupture is usually of the intraperitoneal type and the patient presents as an "acute abdomen". However, the clinical picture may be one of a non-specific peritonitis. The mortality rate is high. We suggest excision biopsy of the edge of the defect in all cases. Intraperitoneal rupture of the bladder following minor trauma has been recorded in children on a few occasions in the past (Bunton, 1952). Stone (1931) reported a remarkable case of a girl with spontaneous extraperitoneal rupture and he made the point that the extraperitoneal rupture is usually insidious in onset. Equally remarkable is our Case 10 in which there were 3 possible causes for rupture following minor trauma, namely that the bladder was neurogenic, chronically infected, and the site of a malignant tumour.

Case 7 is of interest, for more than 100 cases of urethral valves have been treated at this hospital and this is the only one to have presented with a ruptured bladder. Presumably the rupture occurred *in utero*, for the intravenous pyelogram was normal in the neonatal period and at 2 years.

Case 8 shows that should difficulties arise during manual expression of a neurogenic bladder, then this procedure should be abandoned until the outlet resistance had been reduced; in girls this can be achieved by simple dilatation of the urethra.

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* Schering A G, Berlin.

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Life with an Ileal Conduit: Results of Questionnaire Surveys of Patients and Urological Surgeons

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Summary—Two questionnaire surveys were undertaken to investigate the problems experienced by patients and staff in coping with ileal conduits. A survey of 34 patients showed that the major problems were urinary leakage and skin excoriation. In 7 out of 13 patients, leakage was associated with contour problems due to abdominal hernias or recession of the stoma.

Fifty-seven questionnaires were received from British urologists, who each constructed, on average, 7 ileal conduits *per annum.* Twenty of 57 surgeons had no stomatherapist. Leakage and skin reactions were once again the most commonly encountered problems.

It was concluded that the most severe leakage problems could be prevented by careful surgical technique. However, most of the day-to-day problems could be handled by a competent stomatherapist.

Since its popularisation by Bricker in 1950, the ileal conduit has become the most common method of urinary diversion. Much has been written about the technical problems of the operation, but less attention has been paid to the practical difficulties patients face in trying to cope with a new way of life. Adjustment to life with an ileal conduit requires close cooperation between patient, surgeon and nursing staff if the patient is to return to a normal life. To assess the problems experienced by patients and staff, 2 questionnaire surveys were undertaken.

Methods of Survey

Survey of Patients

Thirty-four unselected patients attending the follow-up clinic at the Royal Marsden Hospital were asked to complete a questionnaire. There were 21 men and 13 women, and their ages ranged from 46 to 83 years with a mean age of 65. The indications for surgery are shown in Table 1. The patients completed the questionnaire at home and brought it back at their next clinic attendance where it was checked. No patient refused to participate in the survey.

Survey of Urologists

Fifty-seven completed questionnaires were received from BAUS members out of a total of 151 sent out, a response rate of 38%. Their geographical distribution covered a wide area of the British Isles.

Results

Survey of Patients

We were interested in the patients' knowledge of their condition, and who explained it to them before surgery (Table 2). The majority of those suffering from malignant disease had accurate knowledge about their condition, but it was disturbing to note that none of the patients suffering from non-malignant disease had a clear idea of the reason for surgery. In 27 of 34 cases the pre-operative counselling had been performed by the consultant.

Table 1 Indications for Surgery

Bladder cancer	19
Gynaecological malignancy and fistula	4
Rectal cancer	1
Irradiation cystitis	5
Neurogenic bladder	2
Gynaecological incontinence	2
Prostatic cancer and Crohn's disease	1

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

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Table 2 Pre-operative Counselling

	Bladder condition	*Patients' knowledge*		
		Accurate	*Inaccurate*	*Don't know*
Do you know why you had a stoma made?	Malignant	22	4	5
	Non-malignant	0	1	2
Who explained your operation to you?	Consultant	19	0	8
	Sen. Reg.	1	3	0
	Sister	1	0	0
	Nurse	1	0	0
	Stomatherapist	1	0	0

Twenty-one of 34 patients felt that the quality of their lives had been improved by surgery (Table 3). Not surprisingly, patients suffering from irradiation cystitis or incontinence gained the greatest benefit. However, one patient who had suffered from gross stress incontinence, and a second with a urinary fistula, felt that there had been no change in the quality of their lives.

A survey of the pattern of appliance usage showed 27 of 34 patients had tried more than one appliance. Dislike of the appliance or leakage due to material failure were the reasons for change in 25 of 34 patients. Poor supplies, allergy and fitting difficulties were the reasons given in the remaining 9 cases. Thirty of 34 patients expressed satisfaction with their present appliance.

Only 4 patients felt that their stoma care tuition had been poor, and these had been taught before the services of a full-time stomatherapist had been available. All 28 of 34 patients taught by the stomatherapist expressed satisfaction.

The frequency of bag change is shown in Figure 1. The majority of the patients were able to wear their appliance for 2 to 4 days without changing the bag. Only one patient had to change more than once a day, and he had a very large parastomal hernia. Thirteen of the patients experienced significant problems with urinary leakage and 4 of these had severe problems (Table 4). In 7 of 13, leakage was associated with "contour" problems due to abdominal hernias or recession of the stoma. However, there was no relationship between the length of the stoma and the frequency of bag change (Fig. 2).

Table 3 How Do You Find Life Since Your Operation?

Indications for surgery	*Quality of life*		
	Better	*Worse*	*No change*
Planned trial	5	1	3
Salvage/other disease	6	2	4
Irradiation cystitis	5	0	0
Urinary fistula	3	0	1
Neurogenic bladder	1	0	1
Gynaec. incontinence	1	0	1

Table 4 Problems with Appliance Leakage

Cause	*Minor (>1 per month)*	*Severe (>1 per week)*
Parastomal hernia	1	1
Gulley/recessed stoma	1	2
Night drainage	2	0
Incisional hernia	1	1
Appliance failure	2	0
Unknown	2	0

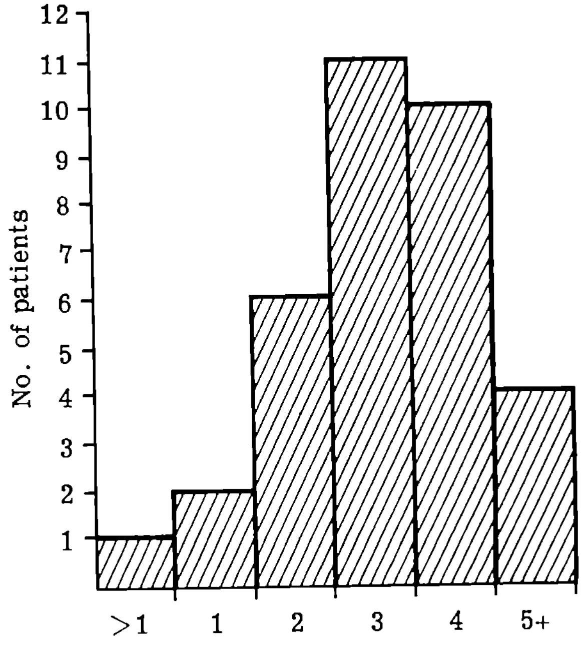

Fig. 1 Frequency of bag change in days.

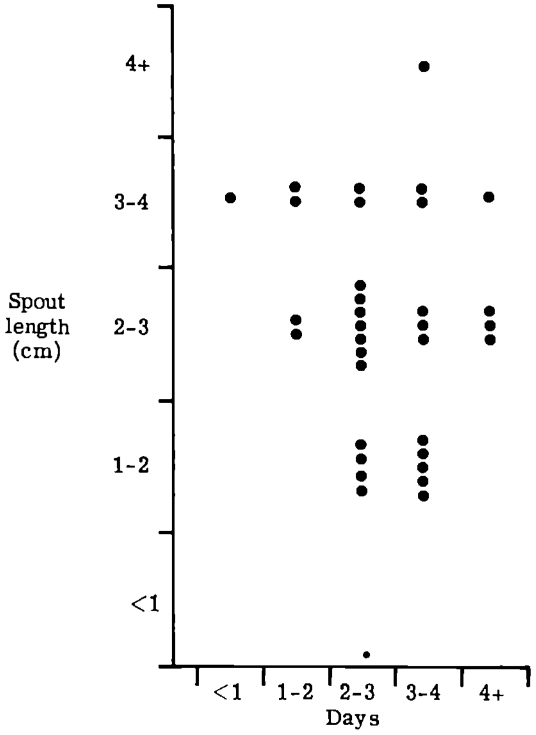

Fig. 2 Frequency of bag change related to stoma length.

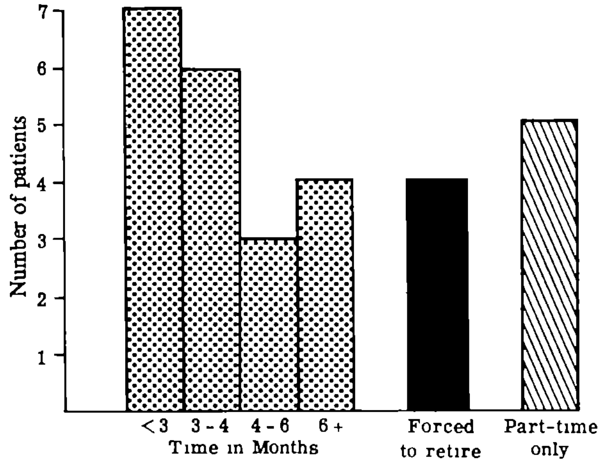

Fig. 3 Time in months before return to work and incidence of partial or complete retirement after operation.

Thirteen of 29 patients who had been at work prior to surgery had returned within 4 months, and all those able to do so had returned at 6 months (Fig. 3). Nine patients were forced to retire or to take part-time work. However, 21 of 34 patients had restricted their social activities since having a stoma. The causes of this were fear of damaging their stoma (9), appliance consciousness (3) and fear of leakage (9). Of the patients sexually active before surgery 6 of 19 men retained some activity, but all were impotent. None of the 3 women previously active resumed sexual activity after surgery, although none had undergone cystectomy.

Survey of 57 Urologists

The number of ileal conduits made in the years 1976 to 1977 and 1977 to 1978 is shown in Table 5. The average number of stomas made per surgeon per year was 7, of which 4 were combined with cystectomy. The 1-year and 5-year survival figures of 82% and 56% indicate an increasing volume of stoma care work in the future. One hundred and twenty-eight admissions were necessary to treat complications arising in these patients: 43 required revision of the stoma and there were 85 other urinary complications.

The appliance training of these patients was performed by stomatherapist (24), nursing sister (39), surgeon (18), appliance fitter (18) and registrar (7). The most popular appliance was the Hollister (Table 6) and 31 of 57 surgeons made it their first choice. Twenty of 51 surgeons had no stomatherapist and 14 of 20 felt that they would like one. Table 7 shows that skin problems and leakage together accounted for over half of all stoma problems. In this survey stones and infection were encountered infrequently. It can be seen that most of the problems (Group I) could have been handled by a competent stomatherapist, and relatively few (11 of 61) required surgical attention (Group II).

Table 5 Number of Ileal Conduits (Survey of 57 BAUS members)

	Number constructed		*Cystectomy (per annum)*	*Children (per annum)*	*Estimated survival (%)*	
	1976-77	*1977-78*			*One year*	*Five years*
Total	402	387	250	36.5		
Average	7.0	6.8	4.5	—	82	56
Range	0-19	0-15	0-13	0-27		

Table 6 Types of Appliances (Survey of 57 BAUS Members)

Appliances	*Types used**	*Surgeon's first preference*
Down's		
Rubber	17	3
Plastic	27	5
Salts		
Rubber	10	3
Plastic	8	3
Coloplast	10	5
Carshalton	2	
Cutifix		
Simpla	6	
Hollister	49	31
Others	2	

* Four used 4 or more types, 23 used 3 or more types.

Ten of 39 surgeons who felt that they would like to participate in a further study identified appliance and skin problems as the areas they would most like to see covered (Table 8). Sixteen of 39 felt that social, family and psychosexual problems had received insufficient attention and merited further investigation.

Discussion

From the figures provided by urologists on the numbers of new ileal conduits they are creating annually, and the numbers of patients expected to live for 5 years, it appears that stoma problems will require increasing time and resources in the future. The most important stoma problems that concerned patients and staff were those of urinary leakage and its consequent skin problems. When severe, the majority of these were found to be related to "contour problems" in our patients, such as recessed stomas and parastomal hernias.

Witherington *et al.* (1977) stressed the importance of correct siting of the stoma and the avoidance of parastomal hernias by careful closure of the abdominal wall. They considered the ideal length of the stoma to be 1 cm, but from our data we would recommend a minimum length of 1 cm. The flush or recessed stoma tends to contract still further and most patients are unable to see it well enough to apply a bag properly (Jeter, 1976). Although some of the wetting problems in our series were caused by appliance failures, the majority of severe "contour problems" could probably have been avoided by closer attention to technical detail in making the stoma.

Table 7 Problems Most Commonly Encountered (Survey of 57 BAUS Members)

Group I—appliance, etc.		*Group II—surgical*	
Skin	19	Retraction	6
Leakage	17	Stenosis	2
Encrustation	4	Hernia	1
Bleeding	3	Stones	1
Supply	2	Infection	1
Fitting	1		
Hair	1		
Allergy	1		
Smell	1		
Psychological	1		

Table 8 Further Studies (Survey of 57 BAUS Members)

Would you like to participate in further study?	Yes 39	No 13
Areas for study		
Appliances, skin		10
Social, family		8
Psychosexual		8
Children, old people		2
Stoma care		2
Cost		1
Surgery, infection		2

In addition to the difficulties of coping with their appliances, patients who have a stoma experience profound psychological changes in the perception of their "body image" (McCawley *et al.*, 1975). Common fears are those of odour, leakage, and loss of sexual attractiveness and performance. Fear was the single feature most important in inhibiting our patients' social lives, and may reflect a failure of explanation on our part.

All of our patients felt that pre-operative discussion of sexual problems had been inadequate and that no guidance had been offered after surgery. Compared to a recent study by Bergman *et al.* (1979), who found that 74% of their patients remained sexually active after cystectomy, our results are disappointing. Although age and general fitness play a large part in the resumption of sexual activity after surgery, the principal inhibiting factors in our patients, particularly the women, were associated with feelings of embarrassment about the stoma or doubts about personal cleanliness.

We conclude that many of the leakage problems associated with the ileal conduit can be eliminated by careful surgical technique. An acceptable quality of life can be enjoyed by patients with an ileal conduit, but aftercare and rehabilitation can be greatly facilitated by close cooperation with a skilled stomatherapist. Further study is needed into the social and psychosexual problems of our patients.

Acknowledgements

We would like to express our appreciation to the patients and members of BAUS who replied to the questionnaires.

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The Prevention of Secondary Haemorrhage after Prostatectomy: the Value of Antifibrinolytic Therapy

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Summary—This study examines the effect of antifibrinolytic therapy on the incidence of secondary haemorrhage following endoscopic surgery.

One hundred consecutive patients were allocated randomly to treatment and control groups. The incidence of secondary haemorrhage was reduced from 56% in the control group to 24% in the treatment group.

Urokinase has been implicated in the impairment of haemostasis in the urinary tract after surgery (McNicol *et al.*, 1961a and b) and the ability of epsilon aminocaproic acid (EACA) to reverse pathological fibrinolytic states has been demonstrated (McNicol *et al.*, 1966). Vinnicombe and Shuttleworth (1966a) demonstrated that this is an effective method of reducing primary haemorrhage after prostatectomy. Secondary haemorrhage is also an important cause of morbidity in patients undergoing transurethral prostatectomy and endoscopic resection of bladder tumours.

Tranexamic acid (AMCA) is a potent inhibitor of plasminogen activators and urokinase, thereby preventing clot lysis, and has been shown to be 8 times more effective than EACA (Anderson *et al.*, 1968). It is a low molecular weight substance which is excreted unchanged in the urinary tract and can be administered both orally and intravenously.

The aim of this trial was to establish whether AMCA was effective in the prevention of secondary haemorrhage.

Patients and Methods

One hundred consecutive patients undergoing transurethral prostatectomy (92) or endoscopic bladder tumour resection (8) were studied. There were 4 bladder tumour resections in each group. The patients with registry numbers ending in even numbers were allocated to the treatment group, those ending in odd numbers were used as controls and received no treatment. The treatment group received tranexamic acid (Cyklokapron-KabiVitrum) 1 g tds for 3 weeks from the first post-operative day.

Four weeks after operation all patients were reviewed and the severity of haemorrhage and its timing were recorded on standard pro formas. Details of duration of haemorrhage and the association of clots were also noted.

A midstream specimen of urine was taken pre-operatively and on the third and twenty-eighth day after operation. Post-operative bacteriuria, when present, was treated with an appropriate antibiotic. Some patients were given antibiotic irrespective of any negative culture results.

The weight of any tissue resected and the haemoglobin level before operation and on the third day post-operatively were recorded.

Results (see Table)

Post-operative Bleeding

Thirteen patients (24%) in the treatment group reported bleeding in the 4 weeks post-operatively, compared to 27 (56%) patients in the control group. This difference is statistically significant ($\chi^2 = 8.9$, $P < 0.01$).

In the treatment group 5 patients (10%) reported bleeding in the second week after operation, 4 (8%) in the third and 6 (12%) in the fourth week. In the control group 20 patients (42%) reported bleeding in the second week, 17 (35%) in the third and 1 (2%) in the fourth week. The first post-operative week was not studied.

Readmission

No patient in the treatment group was readmitted

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Table Analysis of Secondary Haemorrhage

Group	*Number of patients*	*Total bleeders*	*Second week post-op.*	*Third week post-op.*	*Fourth week post-op.*	*Number readmitted*	*Number with clots*	*Number post-op. UTI*
Cyklokapron	52	13	5	4	6	0	6	1
		24%	10%	8%	12%	0	12%	2%
Control	48	27	20	17	1	4	13	3
		56%	42%	35%	2%	8.3%	27%	6%
		$\chi^2=8.9$	$\chi^2=12.02$	$\chi^2=9.95$	$\chi^2=2.13$	$\chi^2=2.60$	$\chi^2=2.97$	$\chi^2=0.35$
		$P=<0.01$	$P=<0.001$	$P=<0.01$	$P=>0.1$	$P=>0.1$	$P=<0.1$	$P=>0.5$

for secondary haemorrhage. Four patients in the control group were readmitted for this reason. This difference is not statistically significant ($\chi^2=2.60$, $P>0.1$) (Fisher's exact probability= 0.10). The 4 patients who were readmitted spent a total of 23 days in hospital.

Clots

In the treatment group 6 patients (12%) reported the passage of clots in the 4 weeks after operation compared to 13 patients (27%) in the control group. This difference was not statistically significant ($\chi^2=2.97$, $P<0.1$).

Urinary Tract Infection

Five patients (10%) in the treatment group and 4 patients (8%) in the control group had pre-operative bacteriuria. At one month only one patient in each group still had proven infection.

Haemoglobin

There was no significant difference between pre-operative and post-operative haemoglobin estimations in either group.

Weight of Resected Tissue

The mean weight of resected material in the treatment group was 17.2 g and in the control group 14.3 g.

Pulmonary Embolism

One patient in each group developed clinical evidence of a deep vein thrombosis. One patient in the control group developed a small pulmonary embolus from which he recovered.

Discussion

The results demonstrate that AMCA markedly reduced the incidence of secondary haemorrhage with its associated morbidity. No patients in the treatment group required rehospitalisation for post-operative bleeding. The 4 patients in the control group spent a total of 23 extra days in hospital at an estimated total cost of at least £1455 (£63.30×23). The cost of 3 weeks' treatment with AMCA is £18.90 per patient, *i.e.* £982.00 for 52 patients. There is, therefore, a sound economic argument for prophylactic AMCA therapy to add to the medical benefits arising from reduced morbidity.

An increased incidence of thromboembolic complications after surgery in the treatment group has not been found in this study. This confirms the conclusions of Vinnicombe and Shuttleworth (1966b) that antifibrinolytic therapy is systematically safe after prostatectomy. However, Ward and Richards (1979) have drawn attention to the possibility of local complications due to indissoluble intravesical blood clots in patients who received AMCA. This was not found to be a problem in our patients, who did not start AMCA therapy until after operation, once the danger of clot retention due to primary haemorrhage was past.

Acknowledgements

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Estramustine Phosphate in the Treatment of Advanced Prostatic Cancer

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Summary—Thirty patients with advanced carcinoma of the prostate were treated with estramustine phosphate. All patients were followed up for a minimum of 9 months.

Of 15 not previously treated with oestrogens 9 responded objectively and 11 subjectively. Of 15 patients whose tumours had failed to respond to at least 2 oestrogens, 3 responded objectively and 5 subjectively.

Adverse effects consisted of cardiovascular complications, gynaecomastia and impotence. Gastrointestinal side effects were minimal and no hepatic, renal or marrow toxicity was seen.

The criteria of assessment of response are discussed.

Patients with advanced carcinoma of the prostate resistant to hormonal treatment have a poor prognosis. Treatment is difficult and results unsatisfactory. They have a mean survival time of about 12 months, or less in cases of metastatic disease.

Because of the relative efficacy of hormones in the treatment of early prostatic carcinoma, urologists had little incentive to pursue other chemotherapeutic approaches. Recently, however, encouraging results of treatment of patients with oestrogen-resistant carcinoma of the prostate with estramustine phosphate (Estracyt) have been reported from Sweden (Alfthan and Rusk, 1969; Nilsson and Jönsson, 1975; Jönsson *et al.*, 1977) and from the USA (Mittelman *et al.*, 1975).

The molecule of estramustine phosphate consists of oestradiol phosphate linked to a nitrogen mustard (Könyves and Liljekvist, 1975).

In the rat, intravenously administered estramustine phosphate is dephosphorylated and concentrated in the ventral prostate (Plym-Forshell and Nilsson, 1974), probably bound to a receptor protein independent of the oestradiol receptors (Appelgren *et al.*, 1977; Forsgren and Högberg, 1977).

Although the mechanism of action of the drug is still unkown, it has been shown to inhibit the activity of 5α-reductase in prostatic tissue in several animal species (Kirdani *et al.*, 1974; Høisaeter, 1975a) and to inhibit thymidine incorporation in rat ventral prostate, both *in vitro* (Høisaeter, 1975b), and *in vivo* (Høisaeter, 1976), more strongly than does oestradiol. In man, about 80% of an oral dose of estramustine phosphate is absorbed from the gut and dephosphorylation occurs during absorption (Plym-Forshell *et al.*, 1976).

The drug is therapeutically active when given by the intravenous or oral route. The former has the disadvantage of occasionally producing local phlebitis and is less convenient for long-term treatment.

It appears to have an affinity for hormone-dependent tissue, but to exert an oestrogenic effect only one-hundredth of that of oestradiol as measured by its uterotrophic effect in the rat (Fredholm *et al.*, 1974), yet against DMBA-induced mammary tumours in rats oestradiol was only 4 times as active as estramustine.

Free oestradiol-17β was absent from all plasma extracts from 3 patients with prostatic carcinoma to whom Plym-Foreshell *et al.* (1976) gave one capsule of estramustine phosphate and assayed the plasma over a 24-h period using a sensitive, specific TLC method. Kadohama *et al.* (1978) found a low level of oestrogenic effects in patients treated with estramustine and from their studies of human prostatic tumour attributed the low plasma levels of oestradiol-17β to successful competition by estramustine phosphate for receptor binding sites. Fossa *et al.* (1977), however, found significant plasma levels of oestradiol during and after treatment with the drug at a dose of 2 to 6 capsules a day, and noted gynaeco-

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mastia in half of their patients. Alexander *et al.* (1979), who reported an objective response to estramustine in 17 out of 39 evaluable cases of advanced, recurrent breast cancer in post-menopausal women, noted vaginal bleeding in only one patient and attributed this to the low systemic oestrogenic activity of the drug.

Von Hoff *et al.* (1977) doubt whether estramustine has any specific effect on human prostatic cancer independent of its oestrogen effect. It has been difficult to discard this objection from the published data available.

The object of the present study was to answer 2 questions:

1. Does estramustine produce an objective response when used as primary treatment in advanced prostatic carcinoma?
2. Does estramustine produce an objective response in advanced prostatic carcinoma which has ceased to respond to oestrogens?

Patients and Methods

Between August 1976 and May 1978 we have treated 50 patients with estramustine phosphate by mouth. We report the results of treatment of 15 patients with newly diagnosed carcinoma of the prostate (Group A) and 15 with oestrogen-resistant prostatic cancer (Group B). No patient had had an orchiectomy. All 30 patients were followed up for at least 9 months.

All patients admitted to the trial had (i) a histologically confirmed carcinoma of the prostate, (ii) a palpable tumour extending outside the prostatic capsule (T3, T4), and (iii) a life expectancy of at least 3 months.

Entry to the Group B study was according to our criteria for oestrogen-resistance: these patients had shown no response to treatment with at least 2 different oestrogens, each given for at least 6 weeks.

All patients were given 2 capsules of estramustine phosphate twice a day (daily dose 560 mg) initially. In previously untreated patients (Group A), dosage was halved in those in whom a sustained response occurred after 3 months. The initial dosage was continued throughout the study in patients with oestrogen-resistant tumours (Group B).

Before the start of estramustine treatment all patients were assessed by clinical examination and by serum biochemical, hormonal, immunological and radiological measures. Patients were re-examined every 6 weeks and serum biochemical measures repeated; other tests were repeated 3-monthly and 6-monthly (Table 1).

The immunological effect of estramustine on 17 patients was assessed by:

1. Cutaneous response to 6 recall antigens (candidin, tuberculin, streptococcus, pertussis, tetanus and diphtheria).
2. Serum immunoglobulin (A, G, M, E).
3. Serum alpha-fetoprotein.

These measurements were made before and 3 months after treatment.

Criteria of Response

An effective anticancer drug must be shown to produce a decrease in size or disappearance of the tumour in a proportion of cases. Relief of pain or improvement in performance status or in abnormal biochemical measurements must not be attributed solely to a specific anticancer effect unless accompanied by tumour regression.

Responses were assessed, using objective and subjective criteria, separately for the primary tumour and for any metastases.

Table 1 Investigations During Estramustine Therapy

(*a*) Before treatment	Blood/chemistry: FBC (including platelets), creatinine, urea, acid and alkaline phosphatase, transaminase and lipids Hormonal: Testosterone, DHT, FSH and LH Immunological: Cutaneous response to recall antigens, immunoglobulins and alphafetoproteins X-ray/scintiscan: Excretion urogram, chest film, bone survey, bone scan and liver scan (when indicated)
(*b*) Every 6 weeks	Blood/chemistry
(*c*) At 3 months	Hormonal Immunological Excretion urogram
(*d*) Every 6 months	Scintiscan Excretion urogram

1. Objective Criteria: (i) primary prostatic tumour—a decrease of at least 50% of prostatic tumour mass as estimated on rectal examination. (Neither reduction in hydronephrosis nor decrease in residual urine was accepted as an objective criterion); (ii) metastases—the presence, progression or disappearance of bone scan or radiological evidence of metastases. (Apparent partial regression of lesions indicated by bone scan or radiological survey was not accepted as an objective criterion since other imprecisely assessable factors may influence the appearances.)
2. Subjective Criteria: (i) complete or partial relief of pain as measured by the patient's analgesic requirement; (ii) improvement in micturition symptoms such as dysuria and urgency; (iii) improvement in performance status.

Results (Tables 2 and 3)

After 3 months, treatment was stopped in patients not responding and continued in those showing a response.

Using these criteria, objective response was seen in 9 of the 15 patients who had received no previous treatment (Group A—Table 2) and in 3 of the 15 patients who were unresponsive to oestrogen therapy (Group B—Table 3).

Table 2 Group A: 15 Patients With No Previous Oestrogenic Therapy—Response to Estramustine Treatment

	No. of patients	*Patients still in remission after 9 months*
Objective response	9/15	6
Subjective response	11/15	7
Analysis of objective responses		
Response of prostatic tumour (partial regression)	9	6
Response of metastases	0	0
Analysis of subjective responses		
Urinary symptoms	10	7
Painful bony metastases (4 patients only)	2	0
In one patient there was amelioration of urinary symptoms and of pain from bony metastases		
Mortality		
One patient died of massive pulmonary embolism 2 months after entry to the trial		

Table 3 Group B: 15 Patients Resistant to Oestrogenic Therapy—Response to Estramustine Treatment

	No. of patients	*Patients still in remission after 9 months*
Objective response	3/15	2
Subjective response	5/15	2
Analysis of objective responses		
Response of prostatic tumour (partial regression)	3	2
Response of metastases	0	0
Analysis of subjective responses		
Urinary symptoms	4	2
Painful bony metastases (4 patients only)	1	0
Mortality		
Four patients died of prostatic cancer before 9 months		

Side Effects (Table 4)

In general, estramustine was very well tolerated. In one patient vomiting was severe enough for treatment to be discontinued but in 5 others with gastrointestinal intolerance, symptoms were acceptable in view of the symptomatic relief. The dose was reduced in one case of thrombophlebitis. Eleven patients had some evidence of cardiovascular disturbance. There was no drug-related myelosuppression.

Estramustine caused some oestrogenic effects. Such effects were already manifest in the patients in Group B (oestrogen-resistant): all of the patients in Group A, too, who were treated primarily with the drug developed gynaecomastia

Table 4 Toxicity of Estramustine Phosphate (560 mg daily by mouth) in 30 Patients

Toxic effect	*Number*	
Hepatic	0	
Renal	0	
Haematological	0	
Gastrointestinal mild	5	
severe	1	
Pulmonary embolism (fatal)	1	36% cardiovascular toxicity
Phlebitis	4	
Myocardial infarction	2	
Water retention	5	
Gynaecomastia (usually mild) (already present in 15 oestrogen-resistant patients)	15/15	
Impotence (in 15 patients who had normal sexual activity before treatment)	14/15	

(mild in most cases) and they usually became impotent (14 out of 15 patients).

Hormone Response

Blood levels of testosterone, dihydrotestosterone (DHT) and follicle-stimulating hormone (FSH) fell constantly after 3 months of treatment (Fig.).

Immunological Effect

There were no significant changes in either the cutaneous response to the recall antigens or in the immunoglobulin levels. Alpha-fetoprotein was not detected in any case. It was noted that the patient deteriorated rapidly in one case in which the cutaneous tests were negative following treatment.

Acid Phosphatase

Sixty-six per cent of the patients with bony metastases and 30% of locally extensive cases (T3) had raised acid phosphatase levels. In half of the patients showing an objective response there was a return towards normal levels.

Discussion

Estramustine produced objective therapeutic effects in 60% of patients with previously untreated advanced prostatic carcinoma. However, it remains to be shown, by a randomised comparative trial, whether estramustine is more effective or produces responses of longer duration, or confers longer survival than oestrogens.

The drug produced objective regression of the prostatic tumour in 20% of established oestrogen-resistant cases.

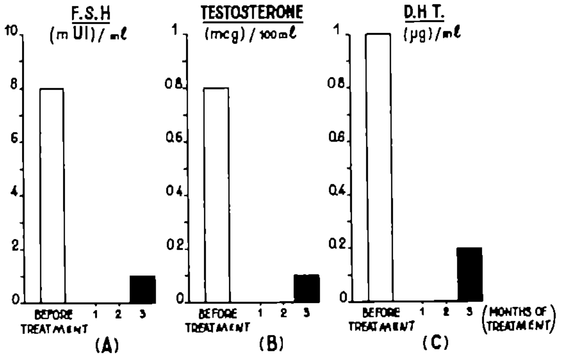

Fig. Blood levels of (*a*) FSH, (*b*) Testosterone, (*c*) DHT after 3 months' treatment with estramustine.

Response was more frequently evident at the primary tumour site than in metastases.

Andersson's review in 1978 of 40 published reports of treatment of a total of 868 patients with advanced carcinoma of the prostate with estramustine indicated a 48% response rate in 597 patients whose cancers had failed to respond to conventional oestrogens and an 84% response rate in 228 patients not previously treated with oestrogens.

The pooling of the results in Andersson's review has the disadvantage that there was some lack of uniformity in the criteria of selection (*e.g.* definition of failure of response to oestrogens) and of assessment of response. The importance of precise, generally acceptable criteria was underlined by Chisholm *et al.* (1977) in their report of experience with estramustine treatment of 30 patients with prostatic cancer progressing in spite of oestrogen treatment or orchiectomy, only 8 of whom achieved a "partial objective response" as defined by stabilisation of disease.

Some of the reports quoted do not include clear and rigid objective criteria in the assessment of response. In particular, a number fail to include adequate information about regression of the palpable primary tumour, an objective response which we believe to be valuable despite the known imprecision in estimating prostatic size even by experienced urologists.

Undue reliance is placed in some of the reviewed reports on the value of changes in the serum acid phosphatase levels as indications of objective response. Evidence of a clear correlation between rise or fall of non-specific acid phosphatase and progression or regression of tumour load is scanty.

Precise definition of "oestrogen-resistance" is usually lacking. Such a definition is important because there are degrees of resistance and responsiveness. Some "oestrogen-resistant" cancers will respond for a time to higher doses of the same drug or to treatment with another oestrogen.

Gastrointestinal side effects from estramustine were minimal in this study. However, there was a significant incidence of cardiovascular complications (36%). It is difficult to assess the role of estramustine in the incidence of these complications without a randomised comparative trial. Jönsson *et al.* (1977) reported cardiovascular complications in 7 out of 154 patients, 5 of whom had advanced heart disease before starting estramustine treatment. Mittelman *et al.* (1975) encountered no cardiac failure or oedema in 32 patients treated at a dose of 7 capsules a day over a 3- to 15-month period.

These results may help to clarify the mechanism of action of estramustine. The drug clearly has an oestrogenic mode of action, as indicated by the drop in plasma testosterone, DHT and FSH, the production of gynaecomastia and the higher rate of response in the non-oestrogen-treated cases compared to the response in the oestrogen-resistant group.

This oestrogenic action does not account for all of the antitumour effect because 20% of the established oestrogen-resistant cases showed a positive response. Thus we must assume that this "extra" action is due either to hormonal action, not of an oestrogenic nature but utilising specific estramustine receptors, or to an antitumour effect which is not dependent on the antigonadotropic action of the drug (Müntzing *et al.*, 1977).

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Chemotherapy of Metastatic Testicular Tumours

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Summary—Results reported in this paper on the use of the combination of vinblastine, bleomycin and cis-platinum in the treatment of 20 patients with metastatic testicular tumours demonstrate that this combination is highly active. All patients demonstrated an unequivocal response to treatment, completeness of response being determined by extent of disease at start of treatment and whether or not patients had received previous treatment with radiotherapy.

Testicular tumours are still the most frequent cause of death in males in the 25 to 35-year-old age group (Registrar General, 1970). Although it has been known since 1960 that metastatic disease does respond to chemotherapy, only about one in 20 of the patients were cured using Actinomycin D alone or in combination (MacKenzie, 1966; McElwain and Peckham, 1974). The introduction of the combination of vinblastine and bleomycin produced long-term cure in about 40% of such patients (Samuels *et al.*, 1976; Peckham *et al.*, 1979). Recent results from America have suggested that the use of cis-platinum in combination with vinblastine and bleomycin increases the long-term cure rate to 60% (though the patients have been followed for only 4 years (Einhorn and Donohue, 1977)). The results presented here are the first on the use of this combination treatment in the United Kingdom.

Patients and Methods

Fifteen patients presenting with metastatic testicular tumours and 5 presenting with metastases after treatment with radiotherapy have been treated. Histology was reviewed by Dr R. C. B. Pugh. All had germ cell tumours but in 4 there was no evidence of teratoma (though 2 of these had raised serum markers suggesting an occult teratomatous element).

Serum markers (beta sub-unit of human chorionic gonadotrophin (β HCG), and alpha-fetoprotein (α FP)) were performed by the supra-regional assay laboratory at St Bartholomew's Hospital, and hydroxybutyric dehydrogenase (HBD) by the biochemistry departments at St Paul's and Hackney Hospitals.

Computerised tomography scanning was performed by Dr Kelsey Fry at St Bartholomew's Hospital.

Treatment Protocol

Table 1 shows the drug treatment which was developed from that reported by Einhorn and Donohue (1977). All except the first 2 patients received 4 courses of induction treatment. Patients had a 10% reduction of vinblastine dosage after the first course of treatment if white blood cell count fell below 1000 per cu mm and platelets below 50,000 per cu mm.

After completion of induction therapy patients without any disease detectable on computerised tomography scan of chest and abdomen received monthly injections of vinblastine 0.3 mg/kg for 12 months.

Patients in partial remission had 3 months' treatment with vinblastine and if disease persisted, surgical exploration and excision were performed if possible.

Table 1 Einhorn BVP Regime for Testicular Tumours

Vinblastine	0.15 mg/k × 2 ↓ ↓		
Cis-platinum	↑ ↑ ↑ ↑ ↑ 20 mg/m^2 × 5		
Bleomycin	↑ 30 mg d2	↑ 30 mg d9	↑ 30 mg d16

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Results

Twenty patients have been treated with a follow-up ranging from 6 to 18 months. With the exception of 2 patients with enormous para-aortic masses and no other disease detectable, all had spread of disease above the diaphragm. Apart from 2 of the patients with pure seminoma (one with bone metastases and one with liver metastases), all patients had evidence of metastatic teratoma.

Patients were assessed for response on the basis of a variety of criteria (Table 2). Two patients who had delayed diagnosis of undifferentiated neoplasm with widespread metastases because no tumour was palpable in the testes died within the first few days of starting treatment and could not be assessed for tumour response. Both had severe electrolyte disturbance prior to death which might have been caused by massive tumour destruction. On the basis of tumour markers, all patients positive before treatment were assessed to have responded as there was complete disappearance of markers for at least 2 months after completion of therapy. Six of 8 patients with disease detectable on chest X-ray had normal chest X-rays after treatment. On computerised tomography scan a further 4 patients had metastases in the chest prior to treatment. After treatment, computerised tomography scans on 8 of these 12 had returned to normal.

Clinically detectable para-aortic disease and supraclavicular disease showed an equally consistent response, with all 9 patients returning to normal after treatment. Computerised tomography scans of the para-aortic region before and after treatment showed a return to normal in 4 of 11 patients whose disease had been detectable before treatment.

The histology of residual tissue in 5 of these with abnormal scans revealed 2 in whom there were no viable tumour cells in the computerised tomography demonstrable mass. A further 2 had all residual disease excised, one a differentiated teratoma and one malignant teratoma intermediate. In a fifth patient it was possible to remove only two-thirds of the tumour because of invasion into surrounding muscle. Computerised tomography of the chest and abdomen was performed before and after treatment on a total of 15 patients, 8 of whom (53%) had a complete disappearance of all detectable disease. Overall, at completion of treatment 10 of 20 patients had no detectable disease on the basis of tumour markers, clinical examination, chest X-ray and computerised tomography scan of chest and abdomen. The response to treatment was better in patients with small amounts of disease, *i.e.* chest X-ray lesions less than 2 cm in diameter and para-aortic mass less than 4 cm in diameter (Table 3). Also of prognostic significance was the rate at which tumour markers returned to normal (Table 4) and whether or not a patient had previous radiotherapy (Table 5).

Table 2 Response to BVP Therapy by Method of Assessment

	N	*Complete response* (%)
Tumour markers	17	100
Clinical assessment of para-aortic and supraclavicular mass	9	100
CXR detectable disease	8	75
EMI scan assessment	15	53
Overall	20*	50 (60)†

* Includes 2 patients who died before response to treatment could be assessed.

† After surgery to the para-aortics.

Follow-up on these patients is too short to establish the long-term outcome. To date, only one of the 10 complete responders has developed a recurrence and one has died in complete remission. This patient, who had previously relapsed after treatment with radiotherapy, died of septicaemia during his fourth course of treatment and at autopsy was found to have no evidence of residual disease. He was treated before we were

Table 3 Influence of Quantity of Disease on Response to BVP Therapy

	N	*Complete response* (%)
Minimal disease at one or more sites	5	4
Advanced disease at one or more sites	15	6 (+2)*

* After surgery to the para-aortics.

Table 4 Influence of Response of Tumour Markers on Eventual Overall Response

	N	*Complete response* (%)
Marker CR after 1st or 2nd course (mean α FP 380 mg/l)	9	89
Marker CR after 3rd or 4th course (mean α FP 1500 mg/l)	6	0 (17)*

* After surgery to the para-aortics.

Table 5 Effect of Previous Radiotherapy on Response to BVP Therapy

	N	*Complete response*	*Current status*		
			Alive and free of disease	*Progressive disease*	*Dead*
Previous DXT	5	2	1	3	1
No previous DXT	15	8 (+2)*	8	2	3

* After surgery to the para-aortics.

aware of the increased toxicity of this regime in patients who had had previous radiotherapy. Four of the 10 partial responders have shown progression of their residual disease but only one has died. The others have had their disease controlled by 3-weekly treatments with cis-platinum combined with the epipodophyllotoxins derivative Vp-16. Apart from one treatment-related death in the first group of patients treated, the complications of treatment have all been controllable. Severe infections requiring intravenous intravenous antibiotics and anaemia requiring transfusions have been the most frequent side effects. Vomiting during the 5 days of treatment with cis-platinum was universal.

Discussion

The results from this study confirm the initial report of Einhorn and Donohue (1977) that the combination of bleomycin, vinblastine and cis-platinum is active in the majority of patients with testicular tumours. In our series it produced an unequivocal response in 100% of cases, and in no other reported series has the response rate been less than 95% (Einhorn and Donohue, 1977; Stoter *et al.*, 1979; Ramsey *et al.*, 1980). The completeness of response was shown to be influenced by the quantity of disease present at the start of treatment and whether the patient had had previous radiotherapy. There is little doubt that this regime is extremely toxic and not the sort of treatment to be given on an occasional basis in a department without experience in its use, or on a routine basis in the treatment of early stages of the disease.

Table 6 Complications in 20 Patients Treated with BVP (×4)

Severe infectious episodes	6
Anaemia requiring transfusion (<9.5 g)	10
Renal failure episodes	3
Vinblastine colic	6

The better results achieved in patients with small volume disease is in agreement with the much more substantial experience of Einhorn who has had only one death from disease in the last 5 years in 112 patients presenting with stages 1 and 2. He followed up patients closely after lymphadenectomy, and treated immediately there was any suggestion of disease progression (Donohue *et al.*, 1978). These results suggest that the best treatment for early stage disease should be close follow-up for the first 2 years at not more than monthly intervals with chest X-ray and tumour markers, and immediate treatment at the first sign of metastases. The relatively poor result achieved with patients who received radiotherapy prior to developing metastases seems to suggest that it would be important to re-evaluate the use of this treatment in patients who present with Stage I disease. It will be important to see if better results can be achieved by giving higher drug dosage to these patients and using intensive supportive care with platelets and granulocyte transfusions and intravenous antibiotics in order to overcome their reduced bone marrow tolerance.

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The Role of Surgery in the Combined Management of Metastases from Malignant Teratomas of Testis

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Summary—Thirty-three patients with malignant testicular teratomas and para-aortic metastases exceeding 2 cm in diameter have been treated with radiotherapy, chemotherapy (vinblastine and bleomycin, with or without cis-platinum) or both, followed by surgical excision of the residual para-aortic mass. Removal of a poorly functioning ipsilateral kidney was necessary in 7 cases (21%) and a segment of vena cava was resected in 2 (12.5%) of 16 patients with primary right-sided tumours. Removal was incomplete in only one patient, who had femoral nerve root involvement, and he subsequently died of secondary haemorrhage (operative mortality 3%).

Undifferentiated tumour was found in 8 (61%) of 13 patients (Group 1) after radiotherapy, compared with only 2 (15%) of 13 (Group 2) after chemotherapy and radiotherapy, and 4 (57%) of 7 (Group 3) who had chemotherapy only prior to surgery; however, 3 of the Group 3 patients were referred because of evidence of activity in the para-aortic region.

The indications for the surgical removal of lymph nodes which may contain metastases from testicular teratomas are controversial. Traditionally, para-aortic lymphadenectomy has been done for diagnostic and therapeutic purposes in most patients treated in North America and in some centres elsewhere, whereas in Britain we have preferred less invasive staging procedures with routine irradiation of para-aortic nodes in early cases, assuming that they may contain microscopic metastases. The latter treatment policy produced results in 275 patients treated at the Royal Marsden Hospital (1962-75) which were as good as those reported from centres doing routine lymphadenectomy, and we preferred this regime because the morbidity was less (Peckham *et al.*, 1977). However, it was clearly recognised that radiotherapy alone could not deal with large volume metastases and that lymphadenectomy might be required in certain carefully selected individuals.

Since the advent of highly effective chemotherapy regimes (Samuels *et al.*, 1976; Einhorn and Donohue, 1977) the prognosis for patients with testicular teratomas has improved greatly, even in the presence of disseminated disease (Donohue *et al.*, 1979; Stoter *et al.*, 1979). This has revived the question: is para-aortic lymphadenectomy necessary as a routine to *select* patients for chemotherapy (Skinner, 1976), or can equally good results be obtained with our policy of routine para-aortic irradiation, keeping chemotherapy for patients who relapse, or who present with bulky or disseminated disease, and reserving lymphadenectomy for excision of residual bulk disease? Twenty-eight (100%) of 28 early stage (I, IIA*) patients treated with radiotherapy at the Royal Marsden Hospital between January 1976 and March 1978 are alive and disease-free at 13 to 37 (median 23) months. Three of these patients (11%) relapsed after irradiation and they remain in complete remission following chemotherapy (Peckham *et al.*, 1979). We believe that, so far, these results justify the belief that lymphadenectomy is unnecessary as a routine in early cases.

The combination of lymphography and ultrasound and, more recently computerised tomography (CT) (Husband *et al.*, 1979) has indicated accurately the presence of para-aortic metastases which were too large (Stage IIB, IIC*) to be treated with radiotherapy alone (Tyrrell and Peckham, 1976). These patients have therefore been treated with chemotherapy and/or radiotherapy, followed by surgical excision of residual bulk disease. In this communication, we describe our experiences with 33 patients treated in this

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

* See Appendix.

Table 1 Pathology of Primary Testicular Tumour Related to Treatment Group

Group	*Number*	*Pathology of testis*		
		TD	*MTI*	*MTU*
1. Old series (1968-76)	13	2	10	1
2. Chemotherapy and radiotherapy (protocol)	13*		7	5
3. Chemotherapy only	7		1	6
Total	33	2	18	12

* Including one seminoma with increased markers.

way since 1968, in order to explore the role of para-aortic lymphadenectomy as part of the combined management of *selected* patients with testicular teratoma.

Patients and Methods

Thirty-two patients had malignant testicular teratomas which were classified according to the British Testicular Tumour Panel (Pugh, 1976); one patient had a primary seminoma of testis with grossly elevated alpha-fetoprotein levels, which were taken as evidence of coexisting malignant teratoma (Table 1). Their ages ranged from 16 to 51 (average 28.9) years. Seventeen primary tumours were on the left and 16 on the right. The patients were investigated pre-operatively by measurement of alpha-fetoprotein and beta-HCG, whole lung tomography, liver scan, lymphography and abdominal ultrasound (Tyrrell *et al.*, 1977), with the addition of CT scanning since 1977 (Husband *et al.*, 1979). The extent of disease was classified by the staging system shown in the Appendix. All 33 patients in this study had para-aortic metastases greater than 2 cm in diameter, and these exceeded 5 cm in diameter in 13 cases. In 10 patients (31%) the disease had extended beyond the para-aortic nodes and in 5 there were distant blood-borne metastases which disappeared with chemotherapy (Table 2).

Table 2 Tumour Stage Related to Treatment Group

Group	*Number*	*Stage**			
		IIB	*IIC*	*III*	*IV*
1. Old series	13	8	2	3	
2. Chemotherapy plus radiotherapy (protocol)	13	2	7	2	2
3. Chemotherapy only	7		4		3
Total	33	10	13	5	5

* See Appendix.

The patients were divided into 3 groups according to the treatment they received prior to lymphadenectomy:

Group 1: Old Series

Thirteen patients treated between 1968 and 1976 received approximately 4,500 rads in 4½ weeks from the 6 MeV linear accelerator to the para-aortic nodes. In addition 6 patients received various combinations of chemotherapy which are now known to be relatively ineffective.

Group 2: Chemotherapy and Radiotherapy

Thirteen ("protocol") patients were treated initially with 2 to 6 courses of chemotherapy. Five patients received vinblastine and bleomycin (VB) (Samuels *et al.*, 1976), 4 had VB with cis-platinum (PVB) (Einhorn and Donohue, 1977), and 4 had both VB and PVB. After a 4-week rest period, they received 4,500 rads in 4½ weeks to para-aortic nodes (6 MeV linear accelerator). A further 4 weeks elapsed after radiotherapy before surgery.

Group 3: Chemotherapy Only

Seven ("non-protocol") patients received 2 to 6 courses of chemotherapy, but *no* radiotherapy. Five patients received PVB and 2 had VB. Three of these patients were treated by Dr Oliver at the Institute of Urology and referred for surgery because of evidence of persisting activity of disease in the para-aortic region (Oliver and Rohatiner, 1979).

The surgical excision was planned after definition of the location and upper limit of the tumour mass by ultrasound or CT scanning (Hendry *et al.*, 1977). A midline incision was used in 23 cases to approach the mass by the technique of Mallis and Patton (1958). In 6 cases a thoraco-abdominal approach (5 left, 1 right) was needed (Skinner and Leadbetter, 1971), whilst a retroperitoneal loin approach was used in 4 patients (Hinman *et al.*, 1923). The excised tissue was fixed in formalin and stained with haematoxylin and eosin.

All patients have been followed at monthly, up to 6-monthly, intervals with regular checking of alpha-fetoprotein and beta-HCG levels and whole

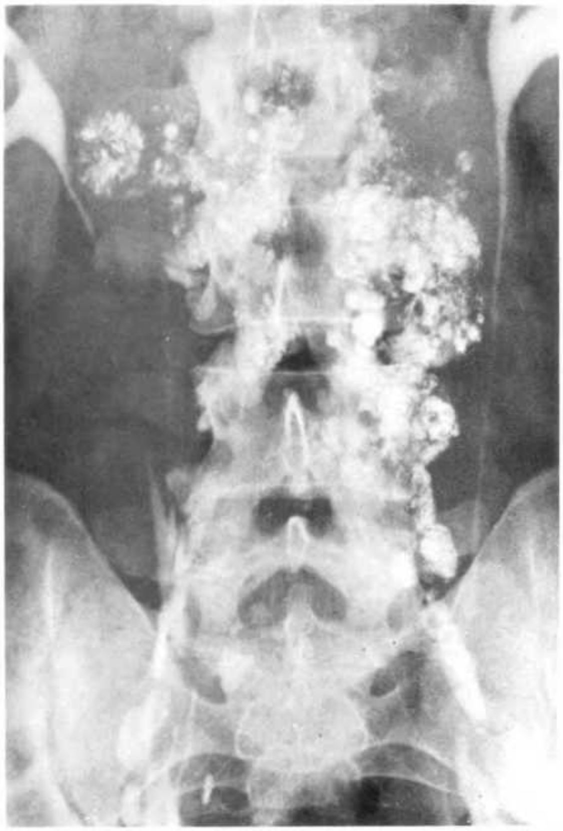

Fig. 1 Diffuse involvement of para-aortic and paracaval lymph nodes originating from a left-sided tumour.

lung tomography, together with at least one postoperative intravenous urogram and abdominal CT scan.

Table 3 Pathological Findings in Excised Lymph Nodes (compare with Table 1)

Group	*Number*	*Pathology of nodes*			
		*NEM**	*TD*	*MTI*	*MTU*
1. Old series	13	1	4	5	3
2. Chemotherapy and radiotherapy (protocol)	13	4	7	1	1
3. Chemotherapy only	7	1	2	1	3

* No evidence of malignancy.

Results

The residual tumour was removed completely in all cases, except for one in Group 2 (see below). The anterior midline incision gave good exposure and always healed well even in irradiated patients. The additional exposure provided by the thoracoabdominal incision was helpful in dealing with the massive tumours. The loin incision was much less satisfactory because of the absence of a posterior plane of cleavage, which limited access to the great vessels. In most cases the mass was discrete and separated from the adjacent structures without undue difficulty. However, in some patients the lymph nodes were diffusely involved (Fig. 1) and in others the mass was very large (Fig. 2). Poorly functioning ipsilateral kidneys had to be removed in 7 cases (3 right, 4 left) because they, or the ureter, were inseparable from the tumour. In 2 cases with right-sided tumours, the vena cava was resected (with preservation of the left renal vein), together with a finger-like projection which extended up towards the heart (Fig. 3). This complication was detected pre-operatively by CT scanning in one case. This was helpful in allowing appropriate arrangements to be made for its removal.

The pathological findings in the excised lymph nodes are shown in Table 3. There was active malignant tissue in 8 (61%) of 13 patients in Group 1. However, in 11 of 13 patients in Group 2, who received chemotherapy and radiotherapy according to the protocol, there was no malignant tissue in the excised nodes, although 7 contained completely differentiated teratoma (TD). There were microscopic foci of active carcinoma in 2 patients (15%), both of whom received the PVB regime. There was active carcinoma in 4 (57%) of 7 cases (Group 3) which received chemotherapy only (2 VB, 2 PVB).

Survival after para-aortic lymphadenectomy is shown in Table 4. Average follow-up is short in Groups 2 and 3; however, very few patients

Table 4 Survival After Para-aortic Lymphadenectomy

Group	*No. alive/ total number*	*No. with disease*	*Survival (months)*	
			Average	*Range*
1. Old series	9/13	1	72	30-120
2. Chemotherapy and radiotherapy (protocol)	12/13*	1	7	1- 27
3. Chemotherapy only (non-protocol)	7/7	1	7	1- 20

* One post-operative death—see text.

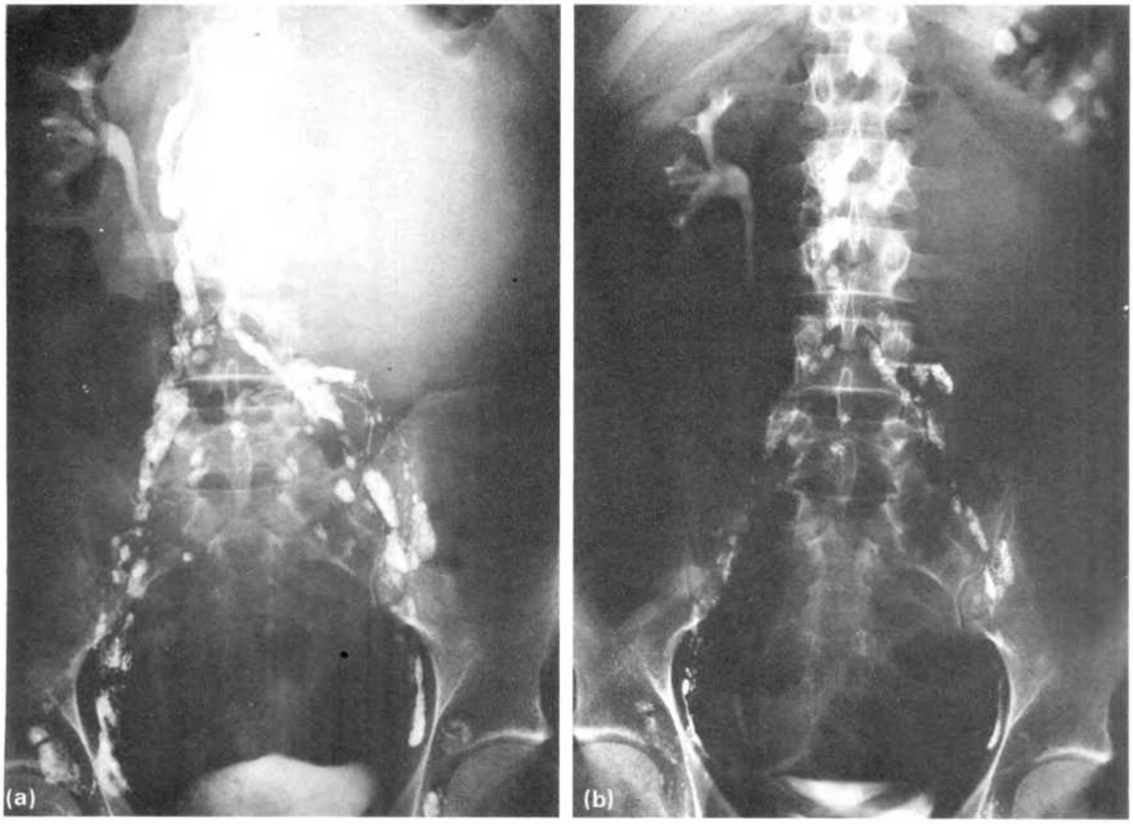

Fig. 2 A very large left-sided tumour mass (a) before and (b) after chemotherapy; although some function returned to the left kidney, nephrectomy was necessary.

have relapsed so far. One patient in Group 2 presented with a massive right-sided tumour and a partially paralysed right leg. This mass was found to have extended through the psoas muscle into the intravertebral foramina where it involved the roots of the femoral nerve. This could not be removed completely and unfortunately this patient died of secondary haemorrhage at 10 days. The operative mortality for this series is therefore 3%. One patient had a deep vein thrombosis, but no other serious complications were encountered. All patients complained of backache for 2 to 3 months and had ejaculatory impotence. Slight transient hydronephrosis was observed in a few patients, but this resolved in all cases by 6 months.

Discussion

There is growing awareness that retroperitoneal lymphadenectomy is not necessary as a routine in early cases of testicular teratoma, either therapeutically or as a staging procedure (Caldwell, 1978). However, it is clear that extensive involvement of para-aortic lymph nodes is an indication for chemotherapy. Our results have indicated that accurate measurement of the *size* of the involved nodes, defined by lymphography and ultrasonography (Tyrrell and Peckham, 1976), is equally as informative as histological examination of excised nodes (Skinner, 1976) in selecting cases for supplementary chemotherapy. The addition of CT scanning has added further precision to the diagnostic imaging of the para-aortic area (Husband *et al.*, 1979). Non-surgical assessment of para-aortic metastases has the considerable advantage that chemotherapy can start without delay, and radiotherapy can be given to an abdomen which is free of post-operative adhesions.

Lymphadenectomy may be beneficial, however, in *selected* patients with bulky metastases in para-aortic nodes, since it is known that chemotherapy is relatively less effective with large volumes of tumour. The question then arises: should surgery precede or follow chemotherapy? Johnson *et al.* (1976) used chemotherapy followed by lympha-

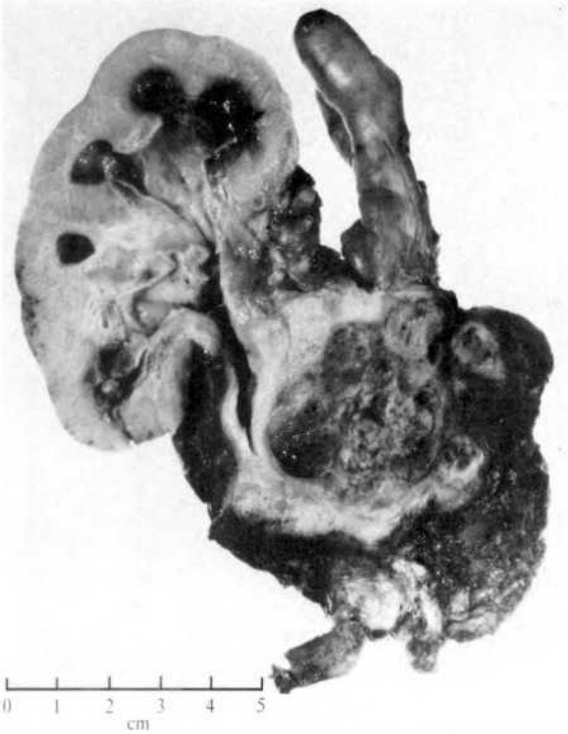

Fig. 3 Metastasis from right-sided tumour involving right ureter and invading vena cava. Note finger-like projection which extended up towards the heart.

denectomy; Merrin *et al.* (1977, 1978) tried it both ways, and concluded that it was best to give intensive chemotherapy first and to reserve surgery for reductive excision of tumour that had not disappeared after 2 months. Donohue *et al.* (1979) supported this view and pointed out that preliminary chemotherapy can debulk the mass prior to surgery, and that the morbidity would be less when operating on a patient in partial remission, as compared with fresh cyto-reductive surgery. Furthermore, the extensive necrosis produced by the chemotherapy should reduce considerably the chance of spillage of viable tumour cells at operation. While the surgical removal of residual para-aortic nodal masses can be undertaken as a re-exploration or second-look procedure after an initial para-aortic exploration has revealed extensive disease (Comisarow and Grabstald, 1976), we believe that the surgical procedure is much easier if it is done as an elective procedure in a previously unoperated abdomen. In addition, the absence of post-operative intestinal adhesions allows us to include radiotherapy as a *pre-operative* treatment option, with minimal risk of radiation enteritis.

The experience gained from the 33 patients described in this paper has shown that even the largest para-aortic metastases from testicular teratomas can be excised after preliminary chemotherapy and/or radiotherapy. Removal of a poorly functioning ipsilateral kidney was necessary in 21% of cases, due to involvement of kidney or ureter. Infiltration of vena cava was found in 2 (12.5%) of 16 cases with right-sided testicular tumours, and so an inferior vena cavogram might be advisable in selected cases to allow arrangements to be made pre-operatively to deal with this complication. The only truly inoperable patient, who unfortunately died, presented with a partially paralysed leg due to femoral nerve root involvement by tumour. This should have been recognised as an ominous sign. The technical details of the operative approach to massive retroperitoneal metastases have been well described by Skinner (1977). We found that careful definition of the exact location of the tumour mass pre-operatively by CT scanning was very helpful in selecting the best surgical approach. Post-operative complications were uncommon, but inevitably some must be expected (Beck and Stutzman, 1979; Sago *et al.*, 1979).

In most cases which had both chemotherapy

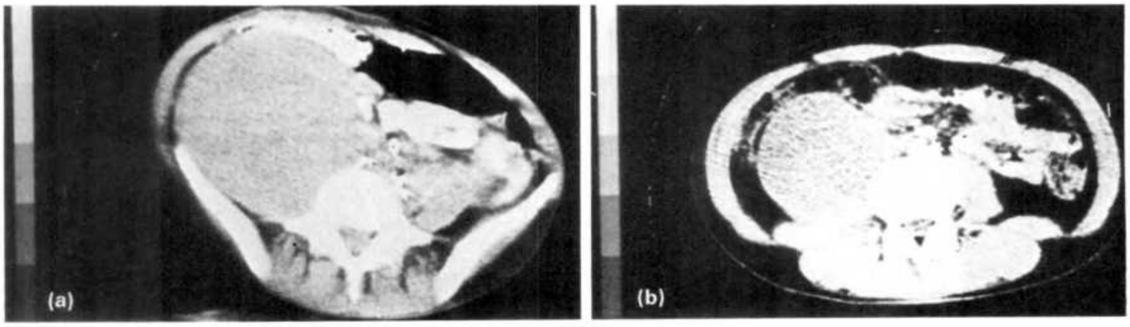

Fig. 4 CT scan of large right-sided para-aortic mass (a) before and (b) after chemotherapy and radiotherapy; this tumour involved the spinal roots of the femoral nerve and excision was incomplete: patient died of secondary haemorrhage.

and radiotherapy, and in some who had only chemotherapy, the excised para-aortic tissue showed no malignancy, or only fully differentiated teratoma. Whether removal of this tissue was necessary therapeutically is not known, but it was not possible to tell pre-operatively which lumps contained tumour and which did not. It is too early to know, yet, whether lymphadenectomy will improve the prognosis for these patients with bulky metastases from testicular teratomas. However, most of these lumps were technically operable, and the time seems ripe for controlled trials of multimodality treatment, amongst which surgical removal of residual bulk disease could reasonably form a part.

Appendix

Staging Classification

Stage:

I Lymphogram negative, no evidence of metastases

II Lymphogram positive, metastases confined to abdominal nodes; 3 sub-groups are recognised:

- A. Maximum diameter of metastases <2 cm
- B. Maximum diameter of metastases 2-5 cm
- C. Maximum diameter of metastases >5 cm

III Involvement of supradiaphragmatic and infradiaphragmatic lymph nodes. No extralymphatic metastases.

Abdominal status

A, B, C as for stage II.

IV Extralymphatic metastases. Suffixes as follows: 0—lymphogram negative, A, B, C, as for Stage II.

Lung status

$L_1 \leq 3$ metastases
L_2 multiple ≤ 2 cm maximum diameter.
L_3 multiple >2 cm diameter

Liver status

H_+ = liver involvement

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The Management of Disseminated Testicular Cancer

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Summary—Fourteen patients with disseminated non-seminomatous germ cell tumours of the testis were treated with a 3-drug combination of vinblastine, bleomycin and cis-diamminedichloroplatinum. Of 13 patients with measurable disease, 9 (69%) had complete and 3 (23%) partial remission. One patient with a solitary metastasis failed to respond but is disease-free following surgical excision. Toxicity was significant but no drug-related deaths occurred and there were no apparent lasting side effects. No patient attaining complete remission has relapsed. Eleven (79%) of the 14 patients are without evidence of disease from 3+ to 36+ months, 6 of these for 2 years or more. Of the patients in partial remission one died at 16 months and one is undergoing further treatment for relapse with liver metastases. One patient remains in partial remission at 30 months. These results demonstrate the efficacy of this drug combination in testicular cancer.

Testicular cancer is the most common malignancy occurring in men in the 20 to 35 age group (MacKay and Sellers, 1966). It is an important disease, although accounting for only 1% of all male cancer. Seminoma, which accounts for about 40% of testicular cancer, is very radiosensitive. Cure rates approach 100% in Stage I (disease confined to the testis) and in Stage II (regional nodes involved) are 70 to 80% (Maier and Sulak, 1973). Non-seminomatous germ cell tumours are less radiosensitive and the relative roles of surgery and radiation therapy remain controversial. Three-year survival for patients treated by retroperitoneal lymphadenectomy or by radiation therapy is 80 to 90% for Stage I and 40 to 80% for Stage II (Staubitz *et al.*, 1974; Maier and Mittemeyer, 1977; Hussey *et al.*, 1977).

Although a 5-year survival rate of 55% has been achieved for metastatic seminoma treated by radiation therapy (Freedman and Purkayastha, 1960), the majority of patients with disseminated testicular cancer will require chemotherapy. Progress in this disease has included the development of new active agents along with their use in combination. In 1976 Einhorn *et al.* presented their initial results using vinblastine, bleomycin and cis-diamminedichloroplatinum (cis-platinum). The present report deals with our experience using a similar drug regime in patients with non-seminomatous germ cell tumours of the testis.

Patients and Methods

Fourteen patients with disseminated non-seminomatous germ cell tumours were the subject of this study. Eight had disseminated disease at initial presentation, while 5 developed metastases within 4 months of completing treatment to the regional nodes. One patient had relapsed following previous complete remission with chemotherapy. Six patients had embryonal carcinoma, 7 embryonal plus teratoma and one embryonal plus choriocarcinoma.

Cis-platinum was given at a dosage of 20 mg/m^2 body surface daily for 5 days, this being repeated at 3-week intervals for 3 courses. Two patients received a fourth course. Patients were hydrated prior to infusion and mannitol 20 G was given with the cis-platinum. Vinblastine was given on days one and 2, 0.2 mg/kg body weight each day, for a total of 5 courses every 3 weeks. In more recent patients the dose of vinblastine has been reduced to 0.15 mg/kg. Bleomycin 30 units I.V. was given intravenously at weekly intervals for 12 weeks. During cis-platinum therapy it was given on day 2, 6 h after vinblastine. Patients achieving complete remission were continued on vinblastine 0.3 mg/kg body weight every 4 weeks. BCG immunotherapy as initially described by Einhorn was not used.

Results

Thirteen patients had measurable disease and of these 9 (69%) achieved complete remission and 3

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Patients with Measurable Disease

No. of patients	*Complete remission*	*Partial remission*
13	9 (69%)*	3 (23%)

* All patients remain in complete remission at 3, 9, 11, 16, 23, 25, 31, 35 and 36 months.

(23%) partial remission (Table 1). None of those in complete remission has relapsed and they remain disease free for 3, 9, 11, 16, 23, 25, 31, 35 and 36 months. Of the 3 patients achieving partial remission, 2 presented with extensive intra-abdominal and pulmonary disease. One died at 16 months from progressive intra-abdominal disease. One had complete remission of multiple lung lesions but persistent minimal intra-abdominal disease for which he received radiation therapy. While completing this he developed liver metastases and is at present receiving further chemotherapy. The third patient presented with jaundice, cachexia and extensive pulmonary lesions (Fig. 1). He remains asymptomatic and in partial remission 30 months later and despite receiving no therapy for 18 months there has been no progression.

One patient with a solitary lung metastasis failed to respond and this lesion was excised. His original testis tumour was mainly embryonal with teratomatous elements. Only teratomatous elements were found in the metastatic lesion, this being mainly cartilage. He remains disease-free 15 months later. One patient did not have measurable disease but was treated because of incomplete resection of intra-abdominal disease. This patient with teratocarcinoma at initial presentation had a large solid mass in the pelvis, extensively involved retroperitoneal nodes and the peritoneal cavity was filled with teratomatous cysts (Fig. 2). These were all resected but fragments of residual tumour remained adherent to pelvis and bowel. He is without evidence of disease 34 months later.

Eleven (79%) patients are without evidence of disease from 3+ to 36+ months, 6 of these for 2 years or more. One patient is dead after a partial remission of 16 months, one remains in partial remission at 30 months and one is being treated for relapse.

Nine patients had elevation of either the serum alpha-fetoprotein, beta subunit of human chorionic gonadotropin or both. In all cases in complete remission these returned to normal and have remained normal. All 3 patients achieving partial remission had gross elevation of both tumour markers initially. In all 3 the markers fell to normal despite evidence of persisting disease. They have remained normal in the patient still in partial remission but became positive prior to the onset of progression of disease in the 2 patients who relapsed.

All patients had nausea, vomiting and alopecia during induction therapy. Severe leukopenia occurred in all patients. Although 3 patients required hospitalisation for granulocytopenia and fever, none had proven sepsis. No patients have demonstrated impairment of renal function from

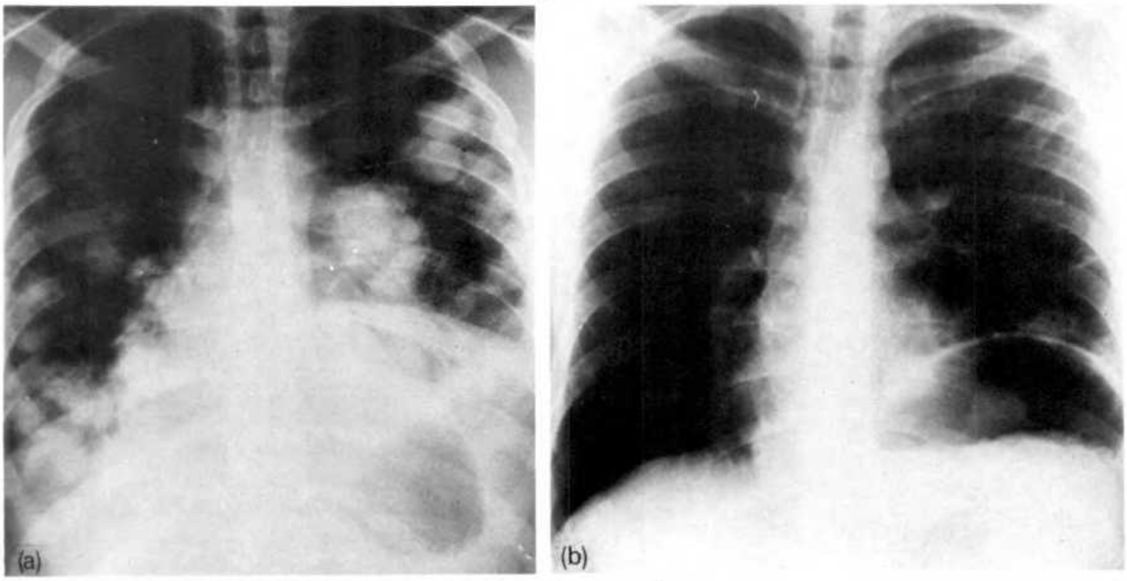

Fig. 1 (a) Chest X-ray prior to treatment. (b) Chest X-ray 30 months later.

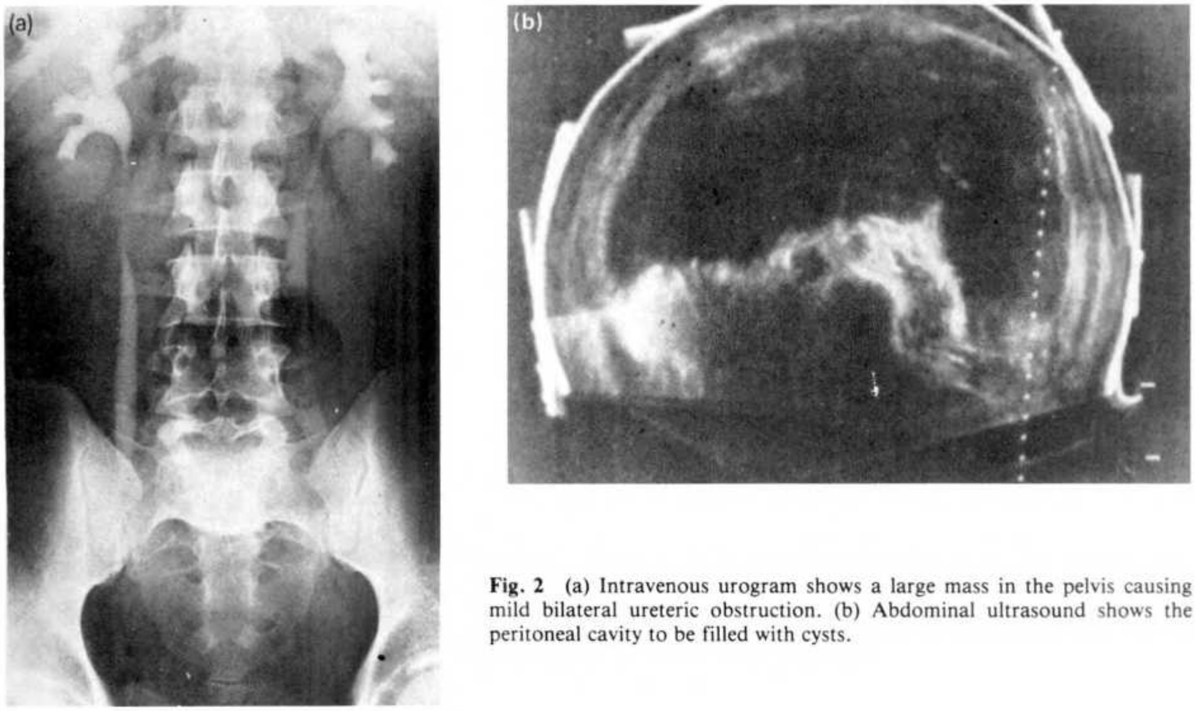

Fig. 2 (a) Intravenous urogram shows a large mass in the pelvis causing mild bilateral ureteric obstruction. (b) Abdominal ultrasound shows the peritoneal cavity to be filled with cysts.

cis-platinum or pulmonary function from bleomycin. Myalgia occurred frequently from vinblastine and this was most severe during the maintenance phase.

Discussion

From 1972 until early 1976, 16 patients with disseminated non-seminomatous germ cell tumours were treated at this institution with a variety of chemotherapeutic agents. Three (19%) achieved complete remission and 2 (13%) partial remission. These results are similar to those reported prior to 1976 (Table 2). In 1976 Cvitkovic *et al.* reported a complete remission rate of 69% using a 5-drug combination of vinblastine, bleomycin, cyclophosphamide, dactinomycin and cis-platinum (VAB III). Einhorn *et al.* (1976), using a 3-drug combination of vinblastine, bleomycin and cis-platinum, reported a 75% complete remission rate. Our present results using vinblastine, bleomycin and cis-platinum are similar and represent a dramatic improvement over our previous experience. None of the 11 patients rendered disease-free has relapsed and 6 of these have been in remission for at least 2 years. Previous experience with testicular cancer indicates that most relapses occur within 2 years (Nefzger and Mostofi, 1972;

Table 2 Chemotherapy of Non-seminomatous Testicular Cancer

Year	*Authors*	*Treatment*	*No. of patients*	*Complete remissions (%)*
1960	Li *et al.*	Dactinomycin, methotrexate, chlorambucil	23	30
1966	MacKenzie	Dactinomycin ± chlorambucil ± methotrexate	154	16
1967	Wyatt and McAninch	Methotrexate	10	40
1970	Mendelson and Serpick	Cyclophosphamide, vincristine, methotrexate and fluorouracil	17	29
1970	Kennedy	Mithramycin	23	22
1975	Samuels *et al.*	Vinblastine, bleomycin	23	39

Lefevre *et al.*, 1975) and it would seem likely that many of these patients will be cured.

While partial remissions to chemotherapy are generally of short duration, it is of interest that one patient has been in partial remission for 30 months. It is probable that these persisting lesions have undergone maturation to a more benign form, as has been previously documented in this disease (Willis and Hajdu, 1973; Merrin *et al.*, 1976). In patients achieving partial response an attempt should be made to eradicate residual disease with surgery supplemented as necessary by radiation therapy.

One unanswered question is whether retroperitoneal lymphadenectomy should be performed in patients who appear to be in complete remission. Three such patients in this series did not receive either surgery or irradiation to regional nodes. In the series reported by Einhorn and Donohue (1977) lymphadenectomy was reserved for those with residual disease. Results to date suggest that further therapy, either surgery or irradiation, may only be necessary when residual disease is suspected or perhaps when bulky retroperitoneal disease is present initially.

Einhorn and Donohue (1977) initially reported a lower response rate for teratocarcinoma as compared to embryonal carcinoma. Further experience, however, has shown similar response rates (Einhorn, 1978). The one patient who failed to respond in the present series had a primary teratocarcinoma with predominantly embryonal elements. The persisting metastatic lesion was teratomatous with no embryonal component. The one patient who died in the present series had some elements of choriocarcinoma. Although choriocarcinoma in combination does not appear to worsen prognosis, results with pure choriocarcinoma are less good (Einhorn, 1978). The present series did not include cases of pure seminoma. Einhorn (1978) has reported complete remission in 9 (69%) of 13 cases of pure seminoma. Although irradiation remains the primary mode of therapy for seminoma, these results indicate that chemotherapy for disseminated disease should be considered before extensive radiation therapy to bone marrow or to lungs has compromised the ability to give these drugs.

Impairment of pulmonary function by bleomycin or of renal function by cis-platinum has not been encountered in this series. Attention to hydration and the use of mannitol appears to help in the prevention of the latter. The most serious side effect was neutropenia, which occurred in all patients. Our policy was to admit and isolate only those patients who were febrile and thought to have possible sepsis. Aminoglycosides should be avoided in these patients as there is a risk of irreversible renal failure when used in patients receiving cis-platinum (US Department of Health, 1978).

We conclude that the combination of vinblastine, bleomycin and cis-platinum can give a complete remission rate of nearly 70% in patients with disseminated testicular cancer. Almost all of the remaining patients will attain partial remission and with adjunctive surgery and/or radiation therapy, some may be converted to complete remission. Relapses to date have been few in those achieving complete remission and eventual cure appears a strong possibility. Toxicity with this regime is significant but was generally well tolerated and no drug-related deaths occurred. No permanent toxic effects have been noted. This combination chemotherapy represents a significant advance in the management of patients with testicular cancer.

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The Doppler Assessment of Varicoceles and Internal Spermatic Vein Reflux in Infertile Men

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Summary—The Doppler technique has been used to evaluate venous reflux in the spermatic cord. Valsalva-induced reflux occurred on the left side in 83% and on the right side in 59% of 118 patients without clinical varicoceles and there was no difference in incidence between fertile and infertile men. The significance of Valsalva-induced reflux should be questioned.

Greater importance should be attributed to the spontaneous venous reflux that occurred during quiet respiration in the majority of patients with varicoceles. Seven velocity waveform patterns are described and these are thought to represent increasing degrees of internal spermatic vein reflux and provide a basis on which it is possible to grade varicoceles. The Doppler grades correlated with the size of the varicocele, and with the internal spermatic vein diameter and testosterone concentrations.

The correction of varicocele by ligation of the internal spermatic vein has become an accepted treatment for male subfertility. The results obtained in a large series of varicocele operations suggest that conceptions occur where even small varicoceles are ligated (Dubin and Amelar, 1970 and 1975). It would therefore seem desirable to diagnose minor degrees of varicocele even though the pathogenesis of the associated infertility remains obscure. The diagnosis of a varicocele depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; these distend when the patient performs the Valsalva manoeuvre. This diagnostic test alone has been used to identify small varicoceles in up to 40% of some series (Dubin and Amelar, 1970; Greenberg *et al.*, 1978), but it has never been scientifically correlated with internal spermatic vein reflux. Hyperactive dartos or cremaster muscles may mimic or mask venous distension of the spermatic cord, and there is difficulty in evaluating the Valsalva test in the absence of an obvious clinical varicocele. There is no universally accepted method for identifying or grading varicoceles, although many systems have been suggested (Uehling, 1968; Steeno *et al.*, 1976). Venography (Ahlberg *et al.*, 1966) and thermography (Monteyne and Comhaire, 1978) have recently been utilised in an attempt to grade and evaluate internal spermatic vein reflux. The Doppler technique has become an accepted non-invasive method for the study of arterial flow (Roberts, 1976). Greenberg *et al.* (1977) used the Doppler technique to study venous reflux in 46 infertile men and suggested that subclinical internal spermatic vein reflux might be more common than previously suspected. We have therefore utilised the Doppler technique as a non-invasive clinical instrument to evaluate venous reflux in the spermatic cords of both fertile and infertile men.

Materials and Methods

In a pilot study of patients with a clinical varicocele which was carried out in the Biomedical Engineering Department of King's College Hospital, the audible characteristics of Valsalva-induced venous reflux were correlated with bi-directional Doppler sonograms (Fig. 1). A 7.7 MHz cardiovascular pocket unit (Sonicaid) was then used to evaluate this phenomenon in erect and supine postures. The Doppler probe was applied with gel contact to the scrotum and the spermatic cord located by audible Doppler flow signals from the testicular artery. The test was scored as positive if a definite venous signal was detected during the Valsalva manoeuvre.

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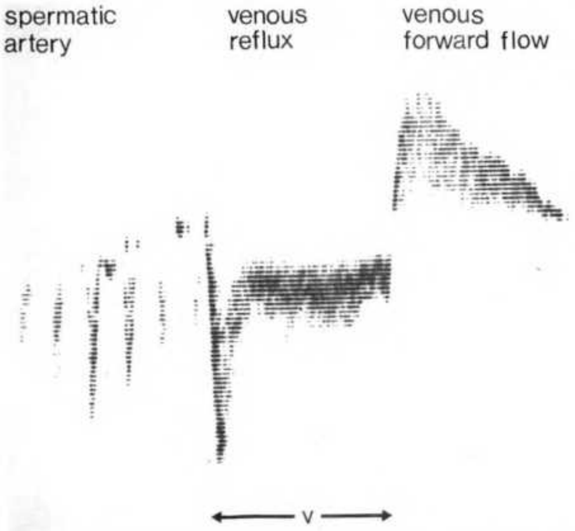

Fig. 1 Directional Doppler sonogram indicating spermatic artery signals and Valsalva-induced venous reflux in the spermatic cord of a patient with a varicocele. Valsalva-induced venous reflux is in the direction of arterial flow and there is forward venous flow once Valsalva ceases (V = Valsalva).

To evaluate velocity waveform characteristics, patients were examined in the erect posture only. The zero crossing output of a Sonicaid BV 380 8 MHz directional velocimeter was coupled to an MX 212 chart recorder (Ormed Engineering) and satisfactory directional velocity tracings were obtained. Recordings were made during quiet respiration and during the Valsalva manoeuvre. The force of the Valsalva manoeuvre was standardised by asking patients to blow into an anaesthetic flow limiter (AGA) set to a pressure of 25 cm of water. Venous activity was monitored in the inguinal canal, scrotum and near the lower pole of the testis (Fig. 2).

Two hundred and sixty-two Doppler assessments have been performed in 2 studies. The first study of Valsalva-induced venous reflux as detected by the pocket unit was made on 44 men with proven fertility (29 pre-vasectomy and 15 volunteers) and 107 infertile men: 10 of the fertile and 23 of the infertile men had clinical varicoceles.

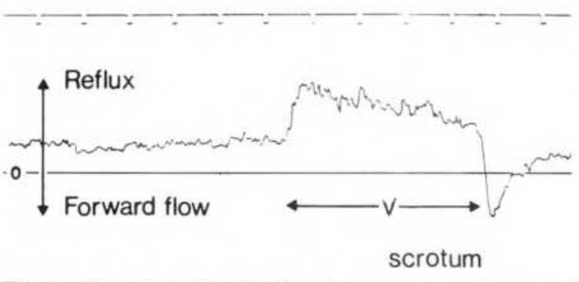

Fig. 2 Chart recording showing the waveform patterns and direction of venous velocity of a left varicocele recorded over the scrotum with a directional Doppler velocimeter (v = Valsalva) time scale: 1 division = 1 s.

In the second study the directional velocimeter was used to study the velocity waveform characteristics of 28 men of proven fertility (8 with varicoceles) and 83 infertile men (37 with varicoceles, 24 without varicoceles and 22 after internal spermatic vein ligation).

The presence of a clinical varicocele was confirmed by examination of each patient in the erect posture for a palpable or visible collection of veins in the spermatic cord and the diameters of both spermatic cords were measured. Each patient was requested to provide a specimen of semen by masturbation after a 3-day period of abstinence.

Internal spermatic vein ligation was carried out as treatment for the varicocele in 40 infertile men and was performed under a general anaesthetic with the patient in a 30 degree feet down position. The inguinal approach was used to identify both the internal spermatic and cremasteric veins. The diameter of the largest internal spermatic vein radicle was measured at the internal inguinal ring, the vein was incised and a cannula was passed proximally and distally in order to collect blood samples; 7 ml of blood was collected from each direction and the anaesthetist simultaneously collected 10 ml of blood from a peripheral vein. The 3 blood samples from each patient were collected in heparinised tubes, the plasma separated and then stored at −20°C prior to assay. The total plasma testosterone level was determined using a conventional liquid phase radioimmunoassay procedure (Collins *et al.*, 1972) with reagents supplied by the WHO Matched Reagents Scheme. Samples from the internal spermatic veins often required dilution in order to obtain accurate values.

At operation the length of each testis was measured (to the nearest 0.5 cm) and small bilateral testicular biopsies were taken; the specimens were placed in Bouin's solution prior to routine embedding and sectioning. The histological sections were stained with haematoxylin and eosin and spermatogenesis was assessed by the Johnsen technique (Johnsen, 1970).

Results

Qualitative Study of Valsalva-Induced Reflux

Table 1 shows the incidence of Valsalva-induced

Table 1 Pocket Doppler Study. Incidence of Valsalva-induced Reflux in Erect or Supine Posture in the Spermatic Cords of 44 Fertile and 107 Infertile Men

	Clinical varicocele			*No varicocele*		
Group	*n*	*Right reflux*	*Left reflux*	*n*	*Right reflux*	*Left reflux*
Fertile	10	9 (90%)	10 (100%)	34	21 (62%)	28 (82%)
Infertile	23	16 (70%)	23 (100%)	84	49 (58%)	70 (83%)
Total	33	25 (76%)	33 (100%)	118	70 (59%)	98 (83%)

reflux in the erect or supine posture. Left-sided Valsalva-induced reflux was demonstrated in all patients with a varicocele but this phenomenon was also found in 83% of patients without varicoceles. Right-sided Valsalva-induced reflux occurred in 63% of spermatic cords without clinical varicoceles. When the results were assessed for Valsalva-induced reflux in the erect posture only, the incidence was 70% on the left side and 49% on the right side for patients without clinical varicoceles.

The incidence of clinical varicocele and Valsalva-induced reflux was similar in both fertile and infertile groups of patients.

Velocity Waveform Characteristics

Examination of tracings from 111 patients has enabled recognition of 7 reproducible velocity waveform patterns (Fig. 3), recorded during quiet respiration and during the Valsalva manoeuvre. The characteristics of these are as follows:

Pattern 0 Showed no venous activity.

Pattern 1 Showed that any venous activity during quiet respiration was too slow to be detected by the Doppler. The Valsalva manoeuvre was associated with a peak followed by a trough on the trace.

Pattern 2 Showed no spontaneous venous activity but venous reflux occurred throughout the Valsalva manoeuvre which was followed by a short trough representing forward venous flow.

Pattern 3 Showed intermittent venous reflux with variation in the intervals between spontaneous venous activity. This was sometimes related to respiration but was often as long as 30 s and was usually increased during the Valsalva manoeuvre.

Pattern 4 Showed continuous venous reflux during normal respiration which was increased during the Valsalva manoeuvre.

Pattern 5 Showed continuous venous reflux which was not significantly increased by the Valsalva manoeuvre.

Pattern 6 Has been recognised only at the inguinal canal. This waveform represents forward flow with cessation during the Valsalva manoeuvre and is the velocity waveform recognised as a normal functioning vein. It was thought to represent secondary cremasteric venous flow at this site, whereas patterns 1 to 5 were thought to represent internal spermatic vein reflux.

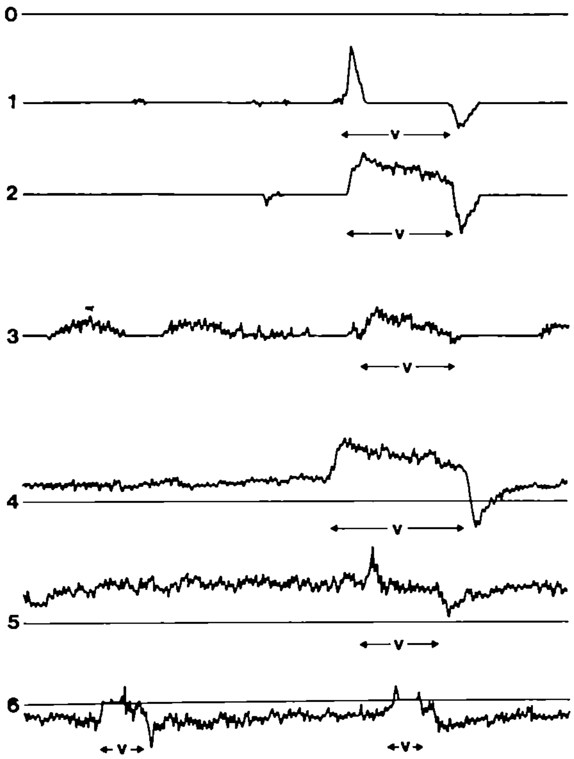

Fig. 3 The 7 venous velocity waveform patterns (V = Valsalva) (see text for explanation).

Grading of Reflux

Since Valsalva-induced reflux was found to be a common phenomenon it was considered more practical to analyse results based on spontaneous venous activity during quiet respiration and these have been graded in the following manner:

Grade I
Waveform patterns 0-2 No spontaneous venous activity
Grade II
Waveform pattern 3 Intermittent reflux
Grade III
Waveform patterns 4-5 Continuous reflux

Technical Aspects of Recording the Doppler Waveforms

The veins in the inguinal canal near the internal inguinal ring lie in a constant position, almost parallel to the examining ultrasonic beam, whereas nearer the testis their course is more tortuous, especially in a patient with a varicocele. Evaluation of the direction of blood flow was therefore more reliable over the inguinal canal, whereas the evaluation of tracings over the scrotum relied more upon sequences and duration of venous activity than the direction recorded. Gentle manual compression of the spermatic cord in the scrotum has been utilised in a searching manoeuvre to assist in locating veins in the inguinal canal where there was no spontaneous venous activity to aid detection.

The sensitivity of the Doppler in detecting venous activity was greater over the scrotum where there was less tissue for the ultrasonic beam to penetrate. Forty-three left varicoceles were analysed according to the site of recording (Table 2). When recorded over the scrotum 91% revealed spontaneous reflux, whereas over the inguinal canal this occurred in only 72% of the same population. The sensitivity of the zero crossing ratemeter to low frequency or low amplitude Doppler shift may be an additional factor, for it was often possible to "hear" venous activity through the headphones of the Doppler although it did not appear on the trace. This is not usually the case with sonographic analyses but these are not widely available because of the cost of the equipment.

Table 2 Comparison of Doppler Grade in 43 Left Varicoceles When Evaluated at Different Recording Sites

	Waveform	*Inguinal canal*	*Scrotum*
Grade I	0-2	12 (28%)	4 (9%)
Grade II	3	22 (51%)	25 (58%)
Grade III	4-5	9 (21%)	14 (33%)

Relationship Between Clinical Observations and Doppler Studies

Incidence of Varicocele

Figure 4 shows the correlation between the 6 Doppler waveforms recognised over the scrotum in 45 patients with a left varicocele and 44 patients without varicoceles. Where a varicocele was present, baseline venous activity was an obvious feature and was usually accentuated by the Valsalva manoeuvre. This baseline activity was rarely observed in the absence of a varicocele.

Only 5 patients with varicoceles did not exhibit spontaneous venous activity during normal breathing, and an additional 8 patients without clinical varicoceles demonstrated spontaneous venous activity (waveforms 3 or 4) during quiet respiration. The latter were thought to represent subclinical internal spermatic vein reflux.

Effect of Operation

Twenty-two patients who had previously undergone ligation of the left internal spermatic vein were evaluated. Five of these had spontaneous venous activity (4 with waveform 3 and 1 with waveform 5) and a further 5 Valsalva-induced reflux (waveform 2). Only one of the patients with waveform 3 had clinical evidence of a recurrent varicocele.

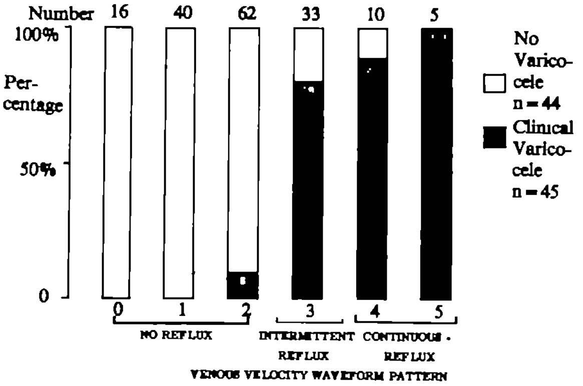

Fig. 4 The incidence of varicocele correlated with the waveform patterns recorded over both spermatic cords in the scrotum of 89 patients, 45 with a left varicocele.

Table 3 Correlation of Doppler Grade Recorded Over the Scrotum and the Difference Between Diameters of the Spermatic Cords in 62 Patients (40 Left Varicoceles)

	Waveform	*n*	*Difference: mean ± SD (cm)*	
Grade I	0-2	24	0.1 ± 0.2	$P<0.001$
Grade II	3	24	0.3 ± 0.2	
Grade III	4-5	14	0.7 ± 0.4	

Relationship Between Doppler Grades and Clinical Findings

Table 3 shows that the measured difference between the diameters of the spermatic cords of the 2 sides increased with increasing Doppler grade. This suggested that there was a higher grade of reflux in the larger varicoceles.

In 30 patients the total number of motile sperms per ejaculate was compared with the Doppler grades. There was no correlation between these variables.

Relationship Between Doppler Grades and Operative Findings

The testis length was measured bilaterally in 31 left varicocele operations and in 10 patients the testes were of equal size. In 17 patients the left testis was smaller and in 3 patients the right testis was smaller. The mean left testis length was 4.1 ± 0.5 cm and the mean right testis length was 4.4 ± 0.5 cm ($P<0.05$). There was no significant correlation between testis length or difference in testis lengths between sides and Doppler grading.

In 28 patients bilateral testicular histology was assessed by the Johnsen method. The mean Johnsen score was not significantly different between the 2 sides (right side 7.4 ± 1.8, left side 7.3 ± 1.9) and there was no correlation with Doppler grading.

The internal spermatic vein diameter was correlated with the pre-operative Doppler grade for the left inguinal canal in 32 patients. The mean internal spermatic vein diameter for patients with grade III (continuous reflux) was 5.4 ± 1.1 mm and this was significantly greater ($P<0.02$) than the mean internal spermatic vein diameters in grade II or grade I varicoceles (Table 4).

Testosterone concentrations in the 3 samples from each patient revealed considerable variation (Table 5). Peripheral values showed a geometric mean and range of 12.1 (3.3—25.3) nmol/l, which were similar to the range established for our laboratory (8.7 – 41.7 nmol/l), and there was no significant difference between subjects with different Doppler grades. The concentrations of testosterone in samples aspirated from the testicular sides of the divided left internal spermatic veins were approximately 100 times greater than in the peripheral plasma—geometric mean and range: 1340.8 (360.2 – 2100.0) nmol/l. The concentrations of testosterone from the renal sides of the internal spermatic veins were intermediate between the values obtained from the other 2 sampling sites and there was a tendency for the mean concentration to decrease with increasing Doppler grade. However, when the Doppler

Table 4 Relationship Between the Diameter of the Internal Spermatic Vein at Operation and Pre-operative Doppler Grade Recorded Over the Left Inguinal Canal (32 patients)

	Waveform	*Diameter of ISV (mm)*		*Significance*
Grade I	0-2	n=9	3.7 ± 1.6	I *v.* II p=NS
Grade II	3	n=13	3.4 ± 1.0	II *v.* III $P<0.001$
Grade III	4-5	n=9	5.4 ± 1.1	III *v.* I $0.02<P<0.01$

Table 5 Comparison Between Left Internal Spermatic Vein Testosterone Concentration and Doppler Grade Detected Over the Left Inguinal Canal (29 patients)

Site of sample	*Grade*	*Waveform*	*Testosterone concentration (nmol/l) geometric mean (and range)*
Testicular side of left internal spermatic vein			1340.8 (360.2-2100.0)
Renal side of left internal spermatic vein	I (n=8)	0-2	116.1 (10.8-881.0)
	II (n=12)	3	48.1 (5.1-753.0)
	III (=9)	4-5	22.4 (12.7-35.3)
Peripheral vein			12.1 (3.3-25.3)

waveform was correlated with testosterone concentration the coefficient of linear regression was poor (r = 0.38).

Cremasteric Veins and Waveform 6

Waveform 6 was recognised late in this series and its incidence over the inguinal canal could be assessed in only 20 patients. Of 9 patients with waveform 6 recorded pre-operatively over the inguinal canal, 8 were found to have secondary dilatation of the cremasteric veins at operation. Where waveform 6 was not demonstrated pre-operatively, 4 out of 11 patients had cremasteric venous dilatation and the mean internal spermatic vein diameter and range of waveform patterns in this group were lower than in the previous group (Table 6).

Discussion

The qualitative Doppler study for Valsalva-induced reflux employs a sophisticated instrument in a simple and highly subjective manner. It may be too sensitive for use in this way. The high incidence of Valsalva-induced reflux in patients without varicoceles was unexpected, and since there was little difference in the incidence between fertile and sub-fertile patients it would appear that the clinical significance of a Valsalva test for the diagnosis of a significant varicocele is questionable.

The possibility of such a high incidence of reflux was suggested by Volter *et al.* (1975) in a post mortem study of the internal spermatic veins. This demonstrated that the variation in morphology and position of valves in the internal spermatic veins would allow reflux on the left in 90% and on the right in 75% of patients without varicoceles. A similar study by Ahlberg *et al.* (1966) reduced these estimates to 50% on both sides. In view of the high incidence of Valsalva-induced reflux it would seem more appropriate to use an assessment method based on spontaneous reflux during quiet respiration.

The directional Doppler technique has enabled the waveform characteristics of venous flow in the spermatic cord to be assessed. The 7 waveform patterns have been arranged in what was considered to be an ascending order of reflux. There are many technical considerations regarding the sensitivity of the instrument, method of recording, interpretation of audible output, recording sites and obesity of the patient, but these variables may be minimised with the use of similar recording sites and identical apparatus.

The 3 Doppler grades of venous reflux provide an additional means for the assessment of a varicocele. The grades represent stasis, intermittent and continuous venous reflux and may be recognised by ear using a non-directional Doppler stethoscope with an audible output. The Doppler technique may also prove to be of value for identifying subclinical venous reflux, the incidence of primary cremasteric venous reflux and the effectiveness of internal spermatic vein ligation.

Increasing Doppler grades of reflux have been shown to be associated with varicocele size, dilatation of the internal spermatic vein and diminution of the concentration of testosterone within the internal spermatic vein which represents a dilutional effect of the reflux.

It has previously been suggested that a varicocele is associated with venous stasis (Ivanissevich, 1960) but the present study more often demonstrates spontaneous venous reflux in the erect posture. This reflux from the left renal vein down the left internal spermatic vein means that blood at core temperature is brought directly into the scrotum. This interferes with the countercurrent heat exchange mechanisms of the pampiniform plexus and may explain why varicoceles are associated with a raised scrotal temperature as has been demonstrated by thermography.

At present the significance of a varicocele in male infertility has yet to be accurately determined but the Doppler technique may provide a simple but accurate non-invasive method for increasing our understanding of this condition.

Acknowledgements

The invaluable technical assistance and advice given by the Department of Biomedical Engineering at King's College

Table 6 The Relationship Between Waveform 6 and Cremasteric Dilatation in 20 Patients with Varicocele

Waveform 6	*n*	*Cremasteric dilatation*	*Range of associated Doppler waveforms*	*Mean ISV diameter (mm)*
Present	9	8	3-5	4.7 ± 1.6
Absent	11	4	1-3	3.7 ± 1.5

Hospital is gratefully acknowledged. We would like to thank the Department of Medical Illustration and Photography at the Institute of Urology for the illustrations, and Mrs J. Boateng for secretarial assistance. This work was supported by a grant from the World Health Organisation.

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Factors Influencing the Outcome of Vasectomy Reversal

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Summary—Fifty-six vasectomy reversals performed during the period 1976 to 1978 have been reviewed with reference to factors which might influence the outcome.

Spermatozoa appeared in the ejaculate in 51 (91%) and remained in numbers greater than 10 million per ejaculate in 35 (63%). The wives of 14 men conceived.

The following factors have been shown to be associated with a favourable result: a short delay between vasectomy and its reversal, a short previously resected segment, opalescent fluid from the cut lower end of the vas and the absence of circulating antisperm antibodies. A substantially higher conception rate was achieved when the husband had remained with his original partner.

Sixty-two testicular biopsies obtained at the time of vasectomy reversal were examined by light microscopy and showed no gross impairment of spermatogenesis. Immunofluorescent techniques failed to show the presence of antigen-antibody complexes in 36 testicular biopsies and in 12 vasal stumps.

Vasectomy has become a popular method for limiting family size and this has been followed by an increase in the number of patients requesting vasectomy reversal. Different surgical techniques have evolved for the operation and there is an increasing trend towards the use of magnification. Using meticulous microsurgical techniques Silber *et al.* (1977) have reported "normal" sperm densities in 90% of patients and 70% of their partners have conceived.

Factors other than operative techniques might be expected to play a part in determining the outcome of vasectomy reversal and this paper attempts to analyse some of these.

Methods

Fifty-six men aged 21 to 44 years (mean 30.7) were admitted to St Peter's Hospital for reversal of their vasectomy between January 1976 and December 1978. The operations were performed under general anaesthesia using a technique similar to that described by Amelar and Dubin (1979).

Sixty-two testicular biopsies were taken at the time of operation and placed in Bouin's solution prior to fixation and examination by light microscopy. Spermatogenesis was assessed by the Johnsen technique (Johnsen, 1970). Thirty-six testicular biopsies were snap-frozen in liquid nitrogen and subsequently examined for the presence of immune complexes by incubation with fluorescein isothiocyanate conjugated antisera and examined microscopically for fluorescence. Antisera to IgG, IgM, IgE, C_3, C_4, and C_{1Q} were used. A control series was obtained from patients having a testicular biopsy in association with varicocele surgery for their infertility. Eight lower and 4 upper vasal stumps were also excised and examined for the presence of immune complexes.

At the time of operation an attempt was made to assess the length and position of the excised segment of vas. The appearance of the fluid from the lower cut end of the vas was also observed.

Blood was obtained pre-operatively and post-operatively for the estimation of the presence of sperm antibodies by the Kibrick technique (Kibrick *et al.*, 1952).

Results

Spermatozoa appeared in the ejaculate of 51 (91%) of our men and the numbers remained above 10 million per ejaculate in 35 (63%). Spermatozoa appeared within one month of operation, but were never above 10 million per

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

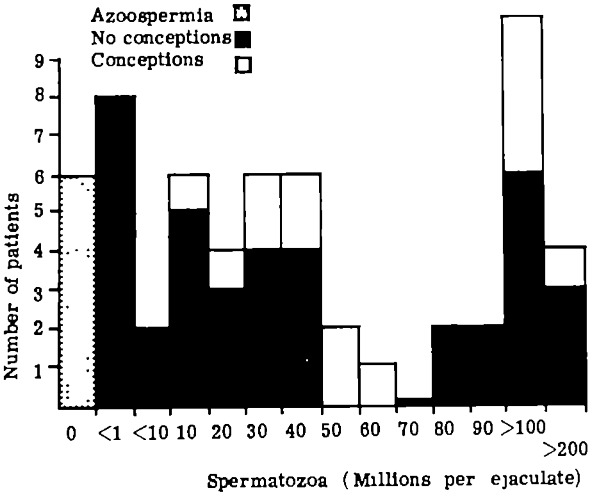

Fig. 1 Relationship between conception and total number of spermatozoa per ejaculate.

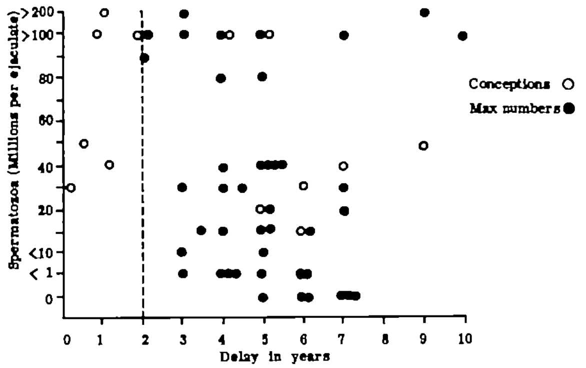

Fig. 2 The effect of delay on the outcome of vasovasostomy.

ejaculate at this time. The numbers subsequently increased so that 80% attained their final "plateau" counts within 6 months. The early appearance of spermatozoa was of no long-term prognostic importance and in 3 patients the initially high numbers of spermatozoa decreased within 6 months, probably as the result of fibrosis around the anastomosis. Fourteen patients' wives had conceived by the time of this review (minimal follow-up 6 months), and 12 of the conceptions occurred within one year of reversal.

Figure 1 shows that conception occurred with equal frequency throughout the range of patients with semen quality better than 10 million sperms per ejaculate. The age of the patients seeking reversal did not appear to have any effect upon the outcome of vasectomy reversal.

Interval Between Vasectomy and its Reversal

Figure 2 shows the maximal density of sperms attained related to the interval between the vasectomy and reversal in years. The wife of every patient who underwent reversal with less than 2 years' delay conceived, and sperm density was higher in patients with delays less than 4 years. Although one conception occurred following a 9-year delay, these figures would seem to be some justification for the statement that a delay of more than 10 years is associated with a poor prognosis (Silber *et al.*, 1977).

Length and Position of Vas Excised

A vasectomy should always be performed above the convoluted part of the vas deferens which lies adjacent to the epididymis. In the present series it was not possible to perform a bilateral vasovasostomy in 5 patients and of these, 2 had unilateral vasovasostomies, 2 bilateral epididymovasostomies, and one a unilateral epididymovasostomy; they maintained counts greater than 200 million, a finding which contrasts with the poor results often obtained by this anastomosis in the treatment of obstructive azoospermia.

The table shows the effect of the length of the resected segment upon the sperm density and conception rate. Although in all of these cases bilateral vasovasostomy was deemed feasible, when the separation was initially longer than 2.5 cm there were only 5 out of 13 counts greater than 10 million per ejaculate. When shorter segments appeared to have been excised, 16 out of 19 counts exceeded 10 million, and these were associated with 5 conceptions. Sperm granulomata were not a feature at the time of our vasectomy reversals.

A greatly dilated appearance of the epididymis, associated with a dry, cheesy material within the lower cut end of the vas, was of universally poor prognostic significance. When opalescent fluid leaked from the lower cut end (N=15) this led to 5 conceptions (33%), confirming this as a good prognostic sign.

Table Effect of the Length of Resected Segment

	Number	*< Ten million*	*> Ten million*	*Conceptions*
Approximated	19	3	16	5
Separated	13	8	5	0

$\chi^2=7.02$, $P<0.01$.

Technical Considerations

Similar patency rates were obtained by the consultant and the surgeons under training, although the former performed more operations where there were recognisable adverse factors.

The operative technique was similar to that described by Amelar and Dubin (1979) and 4-fold magnification was used routinely by one surgeon (J.P.P.). A nylon splint was used only if the anastomosis was technically difficult, and neither the patency nor conception rate of this group differed from those without splints.

Reoperation was universally valuable in selected patients where favourable appearances had been noted at the first operation, and the initially good density of spermatozoa subsequently deteriorated (3 patients). Reoperation on 3 other patients was unrewarding.

Testicular Histology

Light microscopy of 62 biopsies taken from testes one month to 10 years following vasectomy showed the normal spermatogenesis to be well preserved, the average of the mean Johnsen scores being 8.37 out of 10. Impaired spermatogenesis was seen in only 4 biopsies and one of these might be explained by previous inguinal surgery. There was no evidence of transient widespread degeneration of the germinal epithelium as described by Gupta *et al.* (1975).

Circulating Sperm Antibodies

Circulating sperm agglutinating antibodies were detected in titres greater than 1 in 32 in 50% of patients pre-operatively ($N=44$) and 65% post-operatively ($N=46$). Only 2 conceptions occurred with positive tests ($N=26$) against 9 in the negative group ($N=20$). These results show a significant difference ($P<0.01$) and confirm the observation of Sullivan and Howe (1977). In 3 patients a positive pre-operative test reverted to negative after vasectomy reversal.

Deposition of Immune Complexes within the Testis and Vasal Stumps

We were unable to demonstrate the deposition of any immune complexes in the 36 testicular biopsies examined. 1gM and C_3 complexes were identified in 1 out of 6 biopsies taken from patients undergoing varicocele surgery. These patients showed some degree of testicular histological disorganisation. No immune complexes were identified in the 12 vasal stumps examined.

Change of Partner

The fertility of the partner is clearly of importance in determining whether a conception will occur. In men with densities greater than 10 million, 6 conceptions occurred in the 10 with their original partner (60%), while only 7 occurred in the 23 with new partners. It should be noted that those men who remained with their original partner tended to present themselves earlier for reversal.

Discussion

The reversibility of a vasectomy depends upon many factors, and whilst technical expertise is of importance, other factors must also be considered. Many of these should be considered at the time of vasectomy and it is therefore important for urologists to supervise the training of vasectomy surgeons. At the time of vasectomy the vas should be divided well away from the epididymis and the ends placed in different fascial compartments. It is really unnecessary to excise a segment of vas but if any is excised, this should be kept to a minimum.

Much importance has been attached to the immunological aspects of vasectomy and in the present series the number of conceptions was certainly fewer when sperm agglutinating antibodies were detected. The presence of antisperm antibodies did not exclude conception and in some instances the antibody titre fell following the re-anastomosis.

Experiments have shown that the immunisation of males with testicular homogenates or homologous sperm can lead to degenerative testicular changes in a wide range of animals. Following vasectomy in rabbits an orchitis can develop with the deposition of immune complexes and immunoglobulins in the basement membranes of the seminiferous tubules (Bigazzi *et al.*, 1976).

The failure to find antibody in the testicular tissue of our patients may be due to the blood testis barrier, but more interesting is the absence of antibody deposition at the testicular end of the obliterated vas. Studies are currently being undertaken to see whether or not sperm antibodies can be found in the seminal plasma before and after vasectomy reversal. Linnet and Fogh-Anderson (1979) report that antisperm antibodies appeared in the ejaculate of 6 of 37 men following reversal.

Acknowledgements

The authors would like to express their sincere appreciation to Dr Katherine Cameron of the Department of Pathology, Institute of Urology for her review of the testicular histology, and to Dr Paul Evans at the London Hospital for carrying out the Kibrick tests.

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Case Reports

Osteomalacia in Ureterosigmoidostomy: Healing by Correction of the Acidosis

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Osteomalacia may be a late complication of ureterosigmoidostomy (Leite *et al.*, 1966) and it has been suggested that this may require treatment with vitamin D in pharmacological dosage (Harrison, 1958) or 1,25 dihydroxy-vitamin D (Perry *et al.*, 1978). We report a patient successfully treated with alkali therapy.

Case Report

A 60-year-old man had a total cystectomy and ureterosigmoidostomy for bladder carcinoma. He presented 6 years later with bone pain and a proximal myopathy confirmed by electromyography. Serum calcium was 2.02 mmol/l, phosphate 0.65 mmol/l, albumin 40 g/l, alkaline phosphatase 660 iu/l (normal 30-92 iu/l)—95% heat labile, plasma H^+ 51 nmol/l, bicarbonate 7.3 mmol/l, chloride 124 mmol/l, potassium 3.5 mmol/l, urea 12.8 mmol/l, creatinine 145 mmol/l, serum parathyroid hormone (iPTH) 0.66 ng/ml and plasma 25 hydroxyvitamin D (Dr D. E. M. Lawson) normal at 21 nmol/l (8.4 mg/ml). Daily intake of calcium was 35 mmol/l and vitamin D 4.6 nmol. Calcium absorption was 39% (normal). An iliac crest bone biopsy showed severe osteomalacia (osteoid area 19%). The response to the oral administration of 3 g sodium bicarbonate and 3 g potassium bicarbonate daily is shown in the figure. Plasma bicarbonate rose to normal and was accompanied by a rise in serum calcium and phosphate. Serum alkaline phosphatase initially fell and then rose when plasma bicarbonate had reached normal values. The bone pains and proximal myopathy improved after 2 months of alkali therapy. Because of the low dietary intake of vitamin D, oral calcium (20 mmol) and vitamin D_2 50 nmol (800 iu) daily were started. Over the next 10 months alkaline phosphatase fell to 140 iu/l and a bone biopsy performed in June 1976 showed healing of the osteomalacia (osteoid area 5%). Serum calcium and phosphate were unchanged.

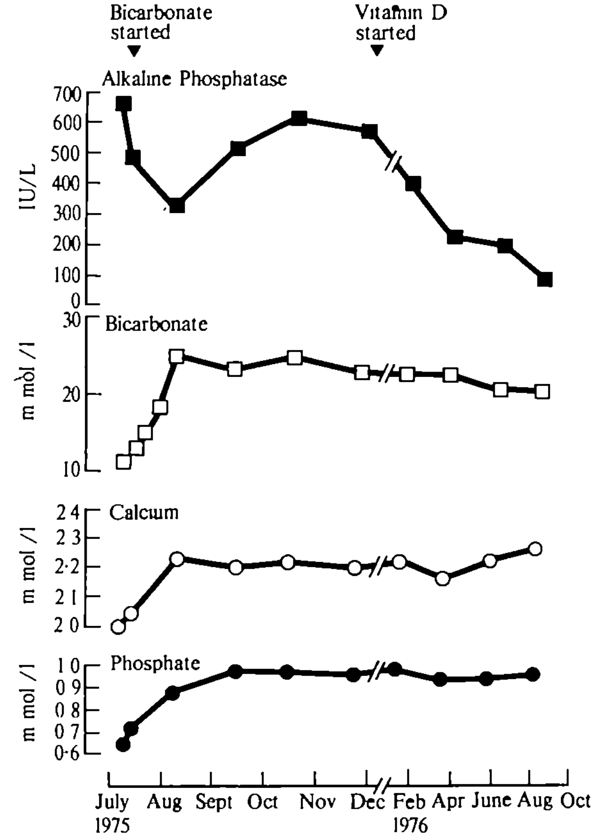

Fig. Biochemical response to alkali therapy. Normal: Calcium 2.0 to 2.6 mmol/l. Phosphate 0.8 to 1.4 mmol/l. Bicarbonate 22 to 28 mmol/l. Alkaline phosphatase 30 to 92 iu/l.

Comment

Correction of the acidosis led to healing of osteomalacia in this patient. Renal 1α-hydroxylation is inhibited by metabolic acidosis (Lee *et al.*, 1977) which may explain the resistance to vitamin D (Harrison, 1958), the success of 1,25 dihydroxy-vitamin D (Perry *et al.*, 1978), and the response to alkali therapy in colocystoplasty (Hossain, 1970). It may, however, take several months of alkali therapy before improvement occurs.

The action of 1,25 dihydroxycholecalciferol in healing all features of osteomalacia is controversial and since it may lead to hypercalcaemia, and possibly deterioration of renal function (Winterborn *et al.*, 1978), we suggest that alkali therapy should be the preferred treatment of osteomalacia following ureterosigmoidostomy.

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Adenocarcinoma of the Pelvis of a Horseshoe Kidney

B. D. PUJARI, M. S. DESHPANDE and M. PHANSOPKAR, *Departments of Surgery and Pathology, Shree Hospital and Miraj Medical Centre, Miraj*

Case Report

A 32-year-old female had had vague digestive disturbances for 6 months which were attributed to a palpable and mobile horseshoe kidney. Three-and-a-half years later she presented with pain and a huge, smooth, non-tender, mobile, well defined cystic lump in the right hypochondriac and lumbar regions. Intravenous pyelography showed dilatation of the lower calices and pelvis of the right half of the horseshoe kidney; the left half was normal (Fig.). During exploration for reconstruction of hydronephrosis, a soft mass was felt in the pelvis with fibrosis of the lower portion of the kidney.

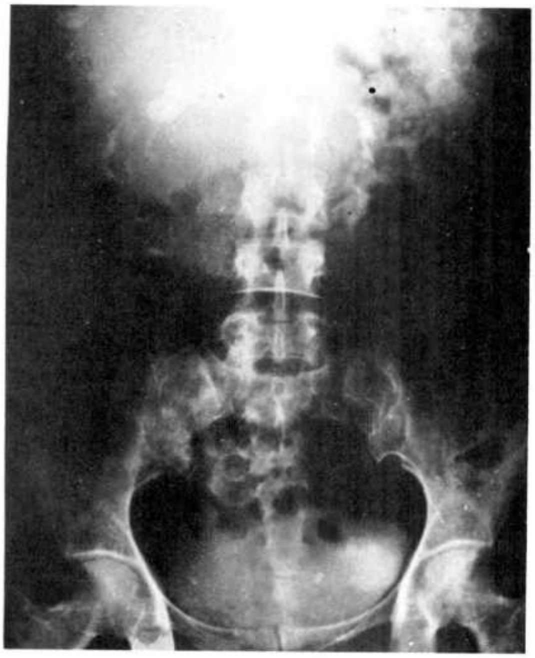

Fig.

A radical right heminephrectomy was carried out. Pathological examination showed mucin-producing adenocarcinoma. A course of deep X-ray therapy was given. The patient has remained well for 1½ years.

Comment

Of the 23 patients with adenocarcinoma of the renal pelvis reported so far, 15 were female and 8 male. This report refers to the youngest patient. The right side was involved in 66% of cases. Common symptoms like pain in the loin, chronic infection and lump had been present for 2 weeks to 20 years (Murphy and Stevenson, 1970). Renal stones and hydronephrosis or pyonephrosis were present in 66% of cases. Stagnation of urine and infection have been postulated as factors responsible for metaplasia and carcinogenesis (Ragins and Rolnieck, 1950). Pitts and Muecke (1975) were surprised to note that despite the high incidence of these complications in the horseshoe kidney, in no case did renal pelvic tumours develop. This is the first reported case of adenocarcinoma of the pelvis of a horseshoe kidney.

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Long Survival after Renal Carcinoma in a Female Child

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Renal carcinoma in childhood is a rare occurrence. Of 100 tumours of the kidney occurring in infancy Riches *et al.*, (1951) noted an incidence of renal carcinoma of 2.6%.

Of 185 cases of renal carcinoma observed over the last 9 years in our department only 2 occurred in patients under 18 years of age.

Case Report

N.E., born in 1960, was first noted to have gross haematuria in October 1968. The haematuria continued and in January 1969 the patient was sent to our department. Excretion urography showed a deformed middle calix with a sickle-shaped appearance, and left retrograde pyelography confirmed the abnormality of the calix.

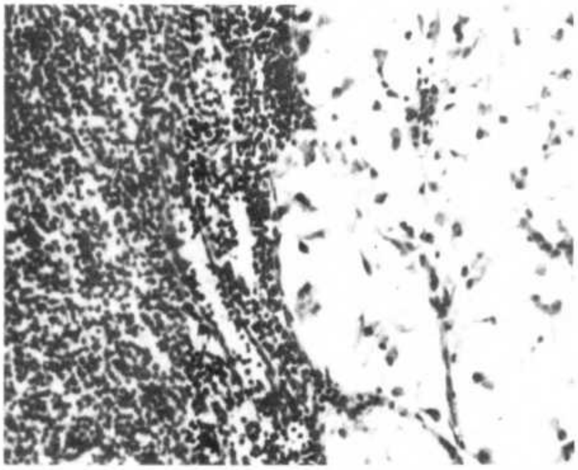

Fig. Lymph node showing renal adenocarcinoma metastases (H and E ×100.)

A scintiscan revealed poor uptake in the upper half of the outer edge of the kidney. Renal angiography was not possible for technical reasons.

At operation a small, yellow, vascular mass was detected in the upper third of the organ. Left nephrectomy was carried out with lymph node dissection. There was no thrombus in the renal vein. *Histological diagnosis*: adenocarcinoma of the left kidney with parahilar lymph node metastases (Stage IIC) (Fig.).

At the most recent follow-up, 8 years later, all investigations were negative.

Comment

Comparison of data on survival of children with renal carcinoma (Castellanos *et al.*, 1974) with those on adults (Robson *et al.*, 1969) shows that at Stages I and III there are no significant differences at 5-year follow-up, whilst at Stages IIA and IIC the survival rate in children is significantly higher than that in adults.

The prolonged survival of the patient described and of other juvenile patients with invasive tumour reported in the literature tends to suggest that renal carcinoma is less malignant in children than in adults.

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Renal Carcinoma in a Child Simulating Post-traumatic Haematoma

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Case Report

V.G., aged 5 years, fell from his bicycle and injured his left flank. Macroscopic haematuria appeared and persisted for some days. Excretion urography showed compression of the calices of the left kidney (Fig. 1) and renal arteriography revealed arterial displacement without an abnormal vascular pattern (Fig. 2). The diagnosis of a post-traumatic haematoma seemed to be confirmed. During the following weeks macroscopic haematuria continued intermittently and when urography was repeated and showed increased caliceal compression, the kidney was explored. There was a small tumour on the lower pole and a nephrectomy was carried out. The tumour was a renal carcinoma. One year later the child remains well and there is no clinical sign of tumour spread.

Comment

Renal carcinoma is extremely rare in childhood. In this patient the injury and initial radiological appearances supported the diagnosis of the renal haematoma. The increase in caliceal compression led to the suspicion of a sinister diagnosis.

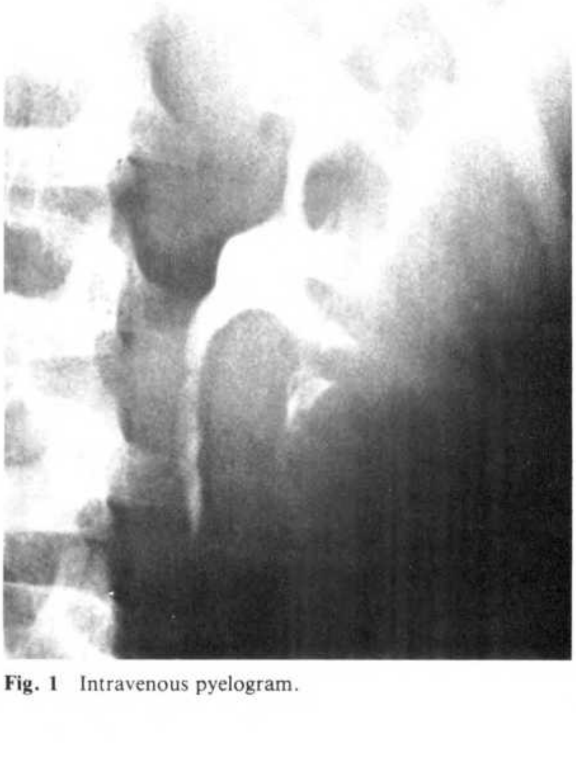

Fig. 1 Intravenous pyelogram.

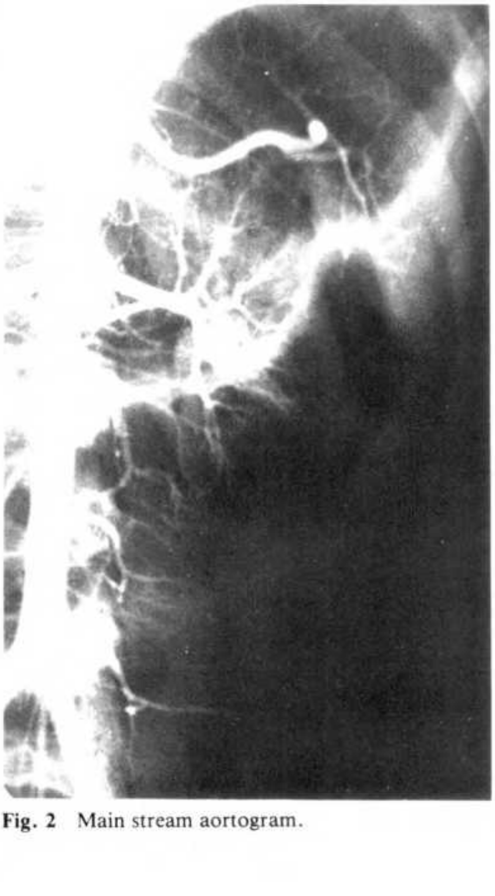

Fig. 2 Main stream aortogram.

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Renojejunal Fistula Caused by Xanthogranulomatous Pyelonephritis

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Case Report

During her first pregnancy in 1974, O.G., aged 27, complained of left renal colic which resolved with antispasmodics. In 1976 she was admitted in the fourth month of a second pregnancy with left renal colic often accompanied by hyperpyrexia. Urine analysis revealed pus and red blood cells with *Staphylococcus* and *Proteus.*

Urography revealed a large calculus in the left ureter, and 15 h after injection a nephrogram of the left kidney was seen.

Left transcutaneous pyelography showed a distended pelvis and calices and reflux of the contrast medium through the upper calix into a jejunal loop. The pregnancy was aborted and a left nephrectomy carried out. The pelvis and calices of the kidney were dilated and filled with pus; a fistula was found between the upper calix and the upper jejunum. Histological examination revealed an obstructive chronic pyelonephritis with a xanthogranulomatous reaction producing perifocal giant cells.

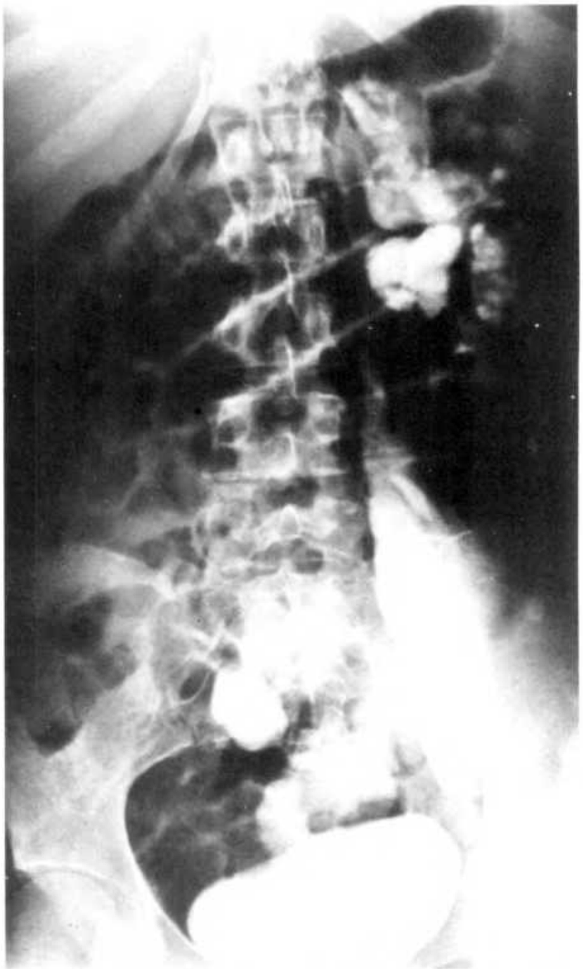

Fig. Left transcutaneous pyelography 30 min after the overall injection of 30 cc of Conray 60%.

Comment

Renojejunal fistulas are extremely rare (Horwich, 1961; Arthur and Morris, 1966) and we know of no case in which it was caused by xanthogranulomatous pyelonephritis (Delsen and Hardmeier, 1976).

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Points of Technique

Self-Retained Balloon Catheters—A Safe Method for Removal

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L. A. WILLIAMS, FRCS, DMRD, FRCR, *Consultant Radiologist, University Hospital of Wales*

A new method is described for the removal of **balloon catheters which cannot be deflated. The** procedure, which was successfully carried out in 6 patients, consists of puncturing the balloon under radiological control.

In the radiology department a cystogram is performed. The catheter balloon is easily seen under the image intensifier and is steadied at the bladder neck by gentle traction on the catheter. A sterile intravenous gauge needle (Fig. 1) is introduced transvesically into the balloon, which immediately bursts (Fig. 2). The bladder is then drained and the catheter removed.

Several methods have been recommended for removing balloon catheters that cannot be deflated (Pitt, 1970; Sood and Sahota, 1972). Some of the methods are potentially dangerous and should not be attempted; others are safe but not always successful.

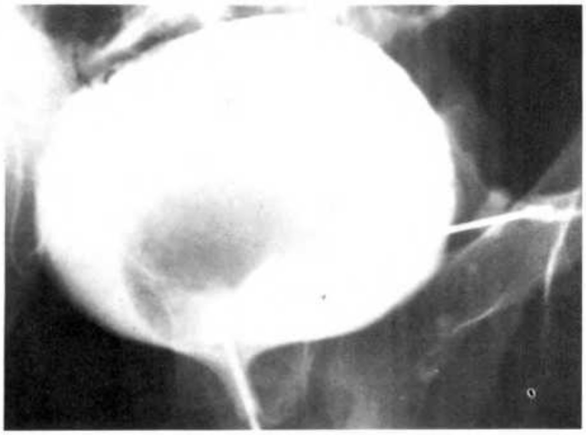

Fig. 1 Cystogram showing catheter balloon and needle prior to puncture.

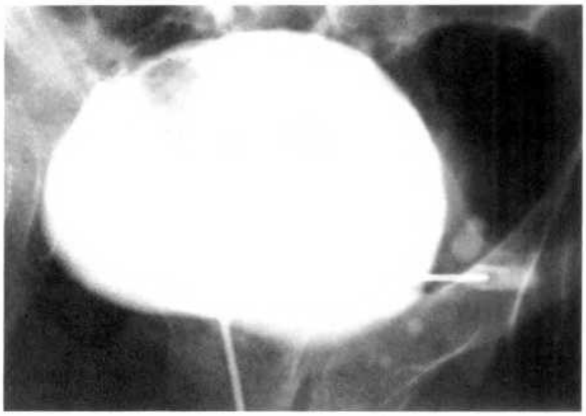

Fig. 2 Cystogram immediately following balloon puncture.

Disruption of the balloon with chemicals such as ether, chloroform or liquid paraffin may cause chemical cystitis, and injection is often not possible because the side arm has been damaged or removed at previous attempts at removal. To burst the balloon by overdistension may require more than 200 ml of fluid.

The procedure described is rapid, reliable, easy and safe.

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Authors' Follow-up

An Evaluation of Otis Urethrotomy in Female Patients with Recurrent Urinary Tract Infections. A Review after 6 Years

D. J. FARRAR, *Department of Urology, Selly Oak Hospital, Birmingham B29 6JD,* N ALAN GREEN and M. HANDLEY ASHKEN, *Department of Urology, Norfolk and Norwich Hospital, Norfolk*

In an earlier study (Farrar *et al.*, 1973) we recommended the use of internal urethrotomy in the treatment of females with recurrent urinary tract infection. We continue to use the Otis urethrotome regularly in the management of these patients with recurrent urinary tract infections and the urethral syndrome. They are often first tried on an Angela Kilmartin "self-help in cystitis" regime (Kilmartin, 1973).

The results continue to be better in cases with proven cystitis rather than those with urgency, frequency and persistently sterile urine. It is accepted that *bougie à boule* urethral calibration is of no functional significance and cannot be used to detect cases which will respond to dilatation.

Otis urethrotomy is still considered a safe procedure, with no incontinence up to a calibre of 40 to 45FG, provided the bladder neck is competent. Otis urethrotomy is, however, not routinely used in females with demonstrable stress incontinence and should be used cautiously in patients with a history of incontinence.

In some cases the Otis urethrotome is used as a calibrated dilator, without using the urethrotomy blade. This minimises urethral bleeding, avoiding the use of a urethral catheter, so that the patient can be treated on a day-stay basis rather than having to remain in hospital overnight.

In cases where there is a persistence of symptoms after an Otis urethrotomy, urodynamic studies are advisable before proceeding to a further empirical urethrotomy. Such studies often reveal the presence of an unstable detrusor which is responsible for the symptoms.

A temporary improvement in urinary symptoms following out-patient cystoscopy and urethral dilatation is still regarded as a reasonable indication for an Otis urethrotomy. Relief of symptoms may be by improving the drainage of paraurethral glands or by a temporary stretch denervation of the urethra.

The authors accept that their use of the Otis urethrotome remains empirical, but it is impractical to carry out urodynamic studies on all females presenting with recurrent cystitis or the urethral syndrome, and the latter remains a distressingly common and unsatisfactory condition.

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Authors' Follow-up

Strontium-87m and the Gamma Camera in the Study of Bone Metastases from Carcinoma of the Prostate. A Review after 6 Years

M. R. G. ROBINSON, *Department of Urology, Pontefract General Infirmary, Pontefract* and A. R. CONSTABLE, *Department of Medical Physics, Institute of Urology, London*

In 1973 we described our experience of bone scintigraphy using the short half-life isotope strontium-87m and the gamma camera in a series of 71 patients with prostatic carcinoma (Robinson and Constable, 1973). It was concluded that this bone-seeking isotope identified osseous metastases in 12% of patients before radiography. Repeated scintigraphy gave some indication of the response to treatment. Healing disease was characterised by a diminished or absent isotope uptake and progressive disease by increased uptake. It was claimed that the gamma camera had an advantage over the scintiscanner in that it produced rapid polaroid photography with little inconvenience to elderly patients with advanced malignant disease. The localisation of disease, however, was crude compared with the scanner and there was no way of making quantitative measurements of isotope uptake.

Since this paper was published, advances in radiopharmacy have given rise to a variety of isotopic agents for use with the gamma camera (Fitzpatrick *et al.*, 1978). These include technetium-polyphosphate, technetium-HEDP and technetium-MDP. Shearer *et al.* (1974) compared technetium-polyphosphate and strontium-87m and concluded that technetium-polyphosphate gave better photography and was more reliable than strontium-87m in the identification of prostatic bone metastases. Gamma camera scintigraphy using technetium-HEDP has been shown by O'Donoghue *et al.* (1978) to have greater accuracy than plasma phosphatases in staging prostatic cancer. Fitzpatrick *et al.* (1978) performed serial scintiscans on 167 patients with prostatic carcinoma using technetium-MDP and demonstrated progression of metastases in 26, regression in 8 and no change in 15. Their criteria for regression were a reduction in the number of hot spots or a 50% decrease in their size. They acknowledged, however, that serial scanning in metastatic disease poses a problem of quantification, and that a computerised facility for assessing successive scans would be an advance.

We believe that our original observations that gamma camera scintigraphy can identify metastases from prostatic carcinoma before conventional radiography, and that follow-up studies of the lesions give an indication of progression or regression, have been confirmed. Strontium-87m has been succeeded by the technetium compounds as the isotope; the gamma camera has been succeeded by more rapid and efficient scintiscanners. There are still problems of quantification when serial studies are performed. The increasing need to evaluate new hormonal and cytotoxic drugs in the management of prostatic cancer makes it essential that further advances should be made in the measurement of progression or regression of this disease.

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Conferences and Courses

Course on Scientific basis of Urological Practice

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13-15 February	Urinary incontinence
18-22 February	Benign prostatic hypertrophy
26-28 February	Urothelial neoplasia
12-13 March	Reconstructive surgery and management of urethral injuries
3-7 March	Andrology

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7-8 March: 2-day course in Urology for the FRCS.
25-26 April: 2-day seminar on Andrology.
May (date to be arranged): 1-day seminar on Renal Disease in Pregnancy.
May (date to be arranged): 3-day course on Transurethral Resection of Prostatic and Bladder Tumours.
6-7 June: 2-day seminar on The Management of Prostatic Neoplasms.
9-13 June: 5-day course on Operative Urology.

Applications to the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Telephone: 01-836 5361, from whom detailed programmes may be obtained.

Edinburgh Urological Festival

Edinburgh. 1-3 September 1980.

A postgraduate course in urology for consultants, senior registrars and registrars. The topics to be covered include: unstable bladder, urethral syndrome, prostatitis, equivocal obstruction, upper and lower tract tumours, investigative techniques, calculi.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG, Scotland, UK.

Basic Urodynamics

Southmead Hospital, Bristol. 11-12 April 1980.

Course topics include Anatomy and Physiology, Basic Techniques, Urodynamic Equipment, Clinical Applications in Urology, Gynaecology and Spinal Injuries.

Further information from: Mr P. H. Abrams, Senior Registrar, Norfolk and Norwich Hospital, St Stephen's Road, Norwich, Norfolk.

Sixth Congress of Yugoslavian Association of Urology

Ohrid, Yugoslavia. 21-24 May 1980.

Official languages—English, French, German, Russian and Yugoslavian.

Further information from: Dr Lj. Vasilev, or Dr A. Stavridis, Surgery Clinic, Department of Urology, Vodnjanska 17, 91 000, Skopje, Yoglslavia.

European Association of Urology: Fourth Congress

Athens, Greece. 28-31 May 1980.

Round Table discussions will be held on:

(i) Surgical treatment of lithiasis.
(ii) New physical methods in urological diagnosis.

Further particulars from: Congress President, c/o Hellenic Promotion Organisation, 36 Voukourestiou Street, Athens 136, Greece.

Symposium on Infection in Surgery

Adelaide, Australia. 29-31 May 1980.

Further information from: Dr V. R. Marshall, Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia 5042.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

British Journal of Urology (1980), 52, 71-72

Book Reviews

Transurethral Resection. Second Edition. Edited by J. Blandy. Pp. vii + 184. London: Pitman Medical, 1978. Price £14.00.

This second edition of Professor Blandy's book on transurethral resection should not be confused with his first edition of 1971. It is now an eminently readable text, covering all aspects of endoscopic surgery in his characteristic and well illustrated style. Each urologist eventually develops his own particular style of resecting: a finger in the (patient's) rectum, the use of the roly-ball electrode, where to start a resection, etc.—all could be debated but here is a clear guide for anyone who wants to learn about a subject which he will then continue to develop throughout his professional career.

Transurethral Resection. Edited by S. J. Silber. Pp. vii + 225. New York: Appleton-Century-Crofts, 1977. Price £13.50.

Dr Silber's book begins with a splendid account of the history of transurethral prostatic resection by Dr Reed Nesbit. The operative technique is described as one of "8 easy steps" and it is no surprise that this is the classic Nesbit method. The illustrations, mainly photographs, are disappointing: some of the pictures are reminiscent of resecting in "the good old days" when the resectionist relied as much on experience as on vision. Nevertheless, it is an authoritative book and well worth reading, preferably after Blandy and certainly after some transurethral experience.

Idiopathic Urinary Bladder Stone Disease. Edited by R. Van Reen. Pp. 370. Fogarty International Center Proceedings No. 37. DHEW Publication No. (NIH) 77-1063. Distributed by Castle House Publications Ltd, Kent, 1977. Price £21.00.

This book contains many articles of interest to the specialist in urinary tract stone disease. The articles are the proceedings of a conference held in 1977. Inevitably some contributions are better than others. Most articles can be found elsewhere, but some of the clinical reports on the incidence of bladder stones from developing countries are more difficult to find. The articles cover such topics as calculogenesis, urodynamics of calculus disease of the upper urinary tract and the absorption, excretion and metabolism of oxalic acid, so that the title of the book is a little misleading, although most of the articles do relate to bladder stones.

Manual of Renal Transplantation. Satya Chatterjee. Pp. xv + 190. Berlin: Springer-Verlag, 1979. Price DM66: $36.30.

This is an attractive-looking volume printed on glossy paper with clear illustrations but the trainee in renal transplantation turning to this manual for a handy, day-to-day guide on the management of patients would be disappointed. The first chapter on "The History of Renal Transplantation" has only 17 column inches (scarcely longer than the references which follow); it is uninformative and commences in the first paragraph with the irritating advice to look elsewhere for information. Similar advice is offered twice more in the first 12 pages. The book picks up interest with 8 concise pages by Dr Gerhart Opelez on "Transplant Histocompatibility". This section is marred by the transposition of "male" and "female" beneath the graphs showing the effect of sex and HLA matching on graft survival. The conflict between text and illustration could confuse the reader who has not seen the information elsewhere. The techniques of vascular access are described in detail, although choice of technique or limb is not. Similarly, lists of post-transplant investigation are offered without guide to their use or interpretation. Complications are described but the clinician with a problem will find little real advice. The author intended to avoid a multi-author volume and had he kept to this view and left out the chapters on dialysis, anaesthesia and psychiatry he would no doubt have written a volume which would justify the present title. As it stands the book is a most readable overview of transplantation for the newcomer to the field but the void indicated in the preface has not, regrettably, been filled.

Pediatric Kidney Disease. Edited by C. M. Edelmann. Volumes 1 and 2. First edition. Volume 1—pp. xxv + 533 + Index 40 pp. Volume 2—pp. xi + 533-1266 + Index 40 pp. Boston: Little, Brown and Company, 1978. Price $35.00 each.

This 2-volume work, written by 101 contributors, sets out to provide a comprehensive account of paediatric nephrology. Volume 1 summarises the background to renal structure and function in health and disease. Each chapter is a review of its subject by an acknowledged expert in his field. Those of practical importance, *e.g.* hypertension and its management, renal failure, growth retardation, are concise, clear and authoritative. The chapter on radionuclide and ultrasound evaluation is likely to be most valuable to clinicians to whom such techniques are relatively new.

Volume 2 contains a systematic description of diseases of the kidneys and urinary tract. To nephrologists the sections on nephritis are of paramount importance. This is dealt with in 13 chapters, some with clinical and some with morphological headings. This is inevitable in an era when the unsatisfactory clinical grouping cannot yet be replaced by a worthwhile aetiological classification. There is surprisingly little repetition but cross reference between several chapters is needed to complete some pictures, *e.g.* the management of the nephrotic syndrome other than the minimal change type.

In the final section on disease in the urinary tract, the chapter on infection presents a clear, balanced and up-to-date view and will be of interest to urologists. The rest of this section will be of more value to nephrologists. It is of necessity brief and a few subjects such as ureterocoele and ectopic ureter are not mentioned. This is an excellent, up-to-date, comprehensive book which will be of great value to everyone concerned with paediatric kidney disease.

Nuclear Medicine in Urology and Nephrology. Edited by P. H. O'Reilly, R. A. Shields and H. J. Testa. Pp. xiii + 201. London: Butterworths, 1979. Prince £15.50.

This book summarises the current views of the Manchester group on the use of radioisotope techniques in urology and nephrology. It is written jointly by a Urologist, a Physicist and a Consultant in Nuclear Medicine.

The first section, on techniques, is apparently written for technicians, and contains detail which will be of little interest to most clinicians. The second section, on clinical applications, is too brief to be of value, whilst the third section on basic principles goes into too much detail. Chapter 16, for example, on mathematics (one of the longest chapters in the book), will be incomprehensible to the majority of clinicians.

In an attempt to be comprehensive, clarity has been sacrificed for brevity, and there are many instances of didactic statements being made without essential qualifications. For example, the description of the sequence of events following acute obstruction appears to be at variance with the general view. The legend of Figure 6.1 is totally misleading. Only passing mention is made of ultrasound and CT scanning in the section on space-occupying lesions of the kidney. Centres which have available to them good quality ultrasound would disagree with most of the conclusions of this chapter.

Although well-printed and produced, this book does not place nuclear medicine in context relative to other investigative modalities and does not do justice to the considerable advances in the subject since 1971, when Britton and Brown published their monograph.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which the papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal.

A general section is included at the end.

ADRENAL

Benign giant adrenal cyst and parathyroid adenoma. (E. R. Katz *et al.*) *J. Urol.* 1979, **121**, 487.

Familial pheochromocytoma: report of 2 cases in kindred. (J. J. Kaufman and S. Franklin.) *J. Urol.* 1979, **121**, 801.

Pheochromocytoma with high blood renin levels. (L. Monnier.) *J. Urol. Néphrol.* 1978, **84**, 892.

Giant adrenal myelolipoma and testicular interstitial cell tumor in a man with congenital 21-hydroxylase deficiency. (D. Boudreaux *et al.*) *Am. J. Surg. Pathol.* 1979, **3**, 109.

Occurrence of nerve fiber in adrenal adenoma and its functional significance. (K. Kano and Y. Togawa.) *Jpn. J. Urol.* 1979, **70**, 358.

Ectopic adrenal in inguinal hernia sacs. (W. T. Gutowski and G. F. Gray.) *J. Urol.* 1979, **121**, 353.

KIDNEY

General. A case of bilateral invagination of normal renal cortex (columns of Bertin). (L. Vlahos *et al.*) *Acta Urol. Belg.* 1979, **47**, 5.

Bilateral cortical necrosis and calcification of the kidneys following snakebite: a case report. (O. A. da Silva *et al.*) *Clin. Nephrol.* 1979, **11**, 136.

Renal localization of sarcoidosis. (F. P. Wambergue *et al.*) *J. Urol. Néphrol.* 1978, **84**, 859.

Atlas of ^{99m}Tc-methylene diphosphonate renal images in pediatric oncology. (J. R. Sty *et al.*) *Clin. Nucl. Med.* 1979, **4**, 122.

Kidney function in acromegaly. (P. C. Eskildsen *et al.*) *Acta Med. Scand.* 1979, Suppl. 624, 79.

Condition of the renin-aldosterone system in patients suffering from hemorrhagic fever and the renal syndrome. (V. F. Bystrovsky.) *Ter. Arkh.* 1979, **51**, 73.

Diagnosis of renal colic in the casualty department. (C. M. Court-Brown.) *Practitioner,* 1979, **222**, 387.

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Evaluation of a new method for treating segmental renal disease. (V. P. Chuang *et al.*) *Surg. Gynecol. Obstet.* 1979, **148**, 739.

Renal pseudoenlargement due to masses in posterior pararenal space. (E. Levine *et al.*) *Urology,* 1979, **13**, 572.

Starling and the ventilator kidney. (M. B. Laver.) *Anesthesiology,* 1979, **50**, 383.

Hypertension due to unilateral parenchymatous nephropathy. (P. Zech *et al.*) *Nouv. Presse Méd.* 1979, **8**, 2173.

Avoiding renal vein entry when implanting the Mobin-Uddin vena cava umbrella filter. (J. K. Edoga and W. D. Widmann.) *Arch. Surg.* 1979, **114**, 752.

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Deposition of ß1H globulin in kidneys of patients with immune renal disease. (J. R. Carlo *et al.*) *Arthritis Rheum.* 1979, **22**, 403.

Patterns of circulating complement in renal diseases. (E. J. Lewis.) *Annu. Rev. Med.* 1979, **30**, 445.

Morphological and immunopathological study of the kidney in Behcet's syndrome. (H. Beaufils *et al.*) *J. Urol. Néphrol.* 1978, **84**, 849.

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The pelvic kidney. Two peculiar cases. (J. Aubert and B. Dore.) *Acta Urol. Belg.* 1979, **47**, 11.

Ectopic kidneys with and without fusion. (B. Kyrayiannis *et al.*) *Br. J. Urol.* 1979, **51**, 173.

Polycystic and horseshoe kidneys in the same family. (R. R. Bailey and M. P. Moore.) *Br. J. Urol.* 1979, **51**, 232.

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Traumatic renal artery occlusion. (R. A. Clark.) *J. Trauma,* 1979, **19**, 270.

Traumatic haematuria in supernumerary hydronephrotic kidney. A case report. (P. I. Øgreid *et al.*) *Scand. J. Urol. Nephrol.* 1979, **13**, 127.

Kidney rupture after transplantation. (G. Cucchiara *et al.*) *Minerva Chir.* 1979, **34**, 287.

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Spontaneous rupture of renal pelvis during postobstructive diuresis. (M. S. Rao *et al.*) *Eur. Urol.* 1979, **5**, 214.

Traumatic caliceal-parenchymal disruption. (R. H. Comisarow *et al.*) *J. Urol.* 1979, **121**, 358.

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Double spontaneous viscero-renal fistula. A report of one case. (M. Caix *et al.*) *Ann. Urol.* 1979, **13**, 45.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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Unilateral emphysematous pyelonephritis. (L. Vlahos *et al.*) *Eur. Urol.* 1979, **5**, 220.

Xanthogranulomatous pyelonephritis in childhood. Report of three cases and a review of the literature. (K. Fahr *et al.*) *Pediatr. Radiol.* 1979, **8**, 10.

Xanthogranulomatous pyelonephritis (XGP): A local disease with systemic manifestations. (M. Goodman *et al.*) *Medicine,* 1979, **58**, 171.

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Bilateral diffuse xanthogranulomatous pyelonephritis. (I. Husain *et al.*) *Br. J. Urol.* **51**, 162.

Tuberculosis of the kidney with arterial hypertension: frequence and evolution according to treatment. (P. Zech *et al.*) *Lyon Méd.* 1979, **241**, 591.

Renal tuberculosis during pulmonary tuberculosis. (J. Salamand *et al.*) *Lyon Méd.* 1979, **241**, 599.

Clinical picture of renal tuberculosis. (P. Deteix *et al.*) *Lyon Méd.* 1979, **241**, 587.

Radiation Nephritis. Urinary kallikrein excretion in idiopathic nephrotic syndrome. (B. H. Brouhard *et al.*) *J. Urol.* 1979, **121**, 672.

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Nephrotic syndrome in procainamide induced lupus nephritis. (P. Zech *et al.*) *Clin. Nephrol.* 1979, **11**, 218.

Calculi. Immunological and bacteriological studies in chronic pyelonephritis associated with kidney stones. (F. P. Schena *et al.*) *Nephron,* 1979, **23**, 162.

Operative versus non-operative management of patients with staghorn calculi and neurogenic bladder. (N. L. Constantinople *et al.*) *J. Urol.* 1979, **121**, 716.

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Surgical management of renal staghorn calculi by selective hypothermic perfusion. (A. Kyriakidis *et al.*) *Eur. Urol.* 1979, **5**, 173.

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115 cases of neonatal renal lithiasis. (R. Cohen.) *Rev. Pediatr.* 1979, **15**, 291.

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Localized cystic disease of the kidney—angiographic-pathologic correlation. (K. J. Cho *et al.*) *Am. J. Roentgenol.* 1979, **132**, 891.

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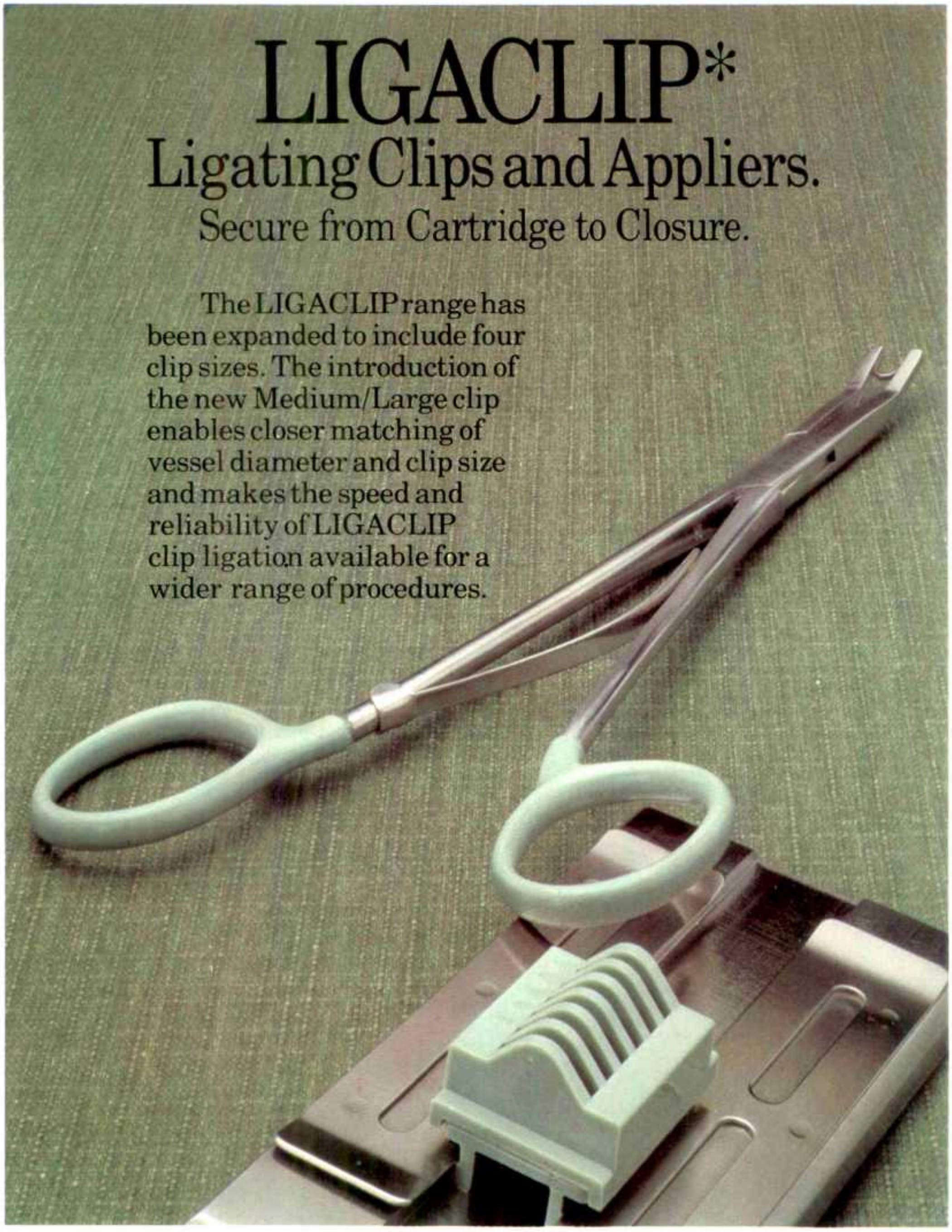

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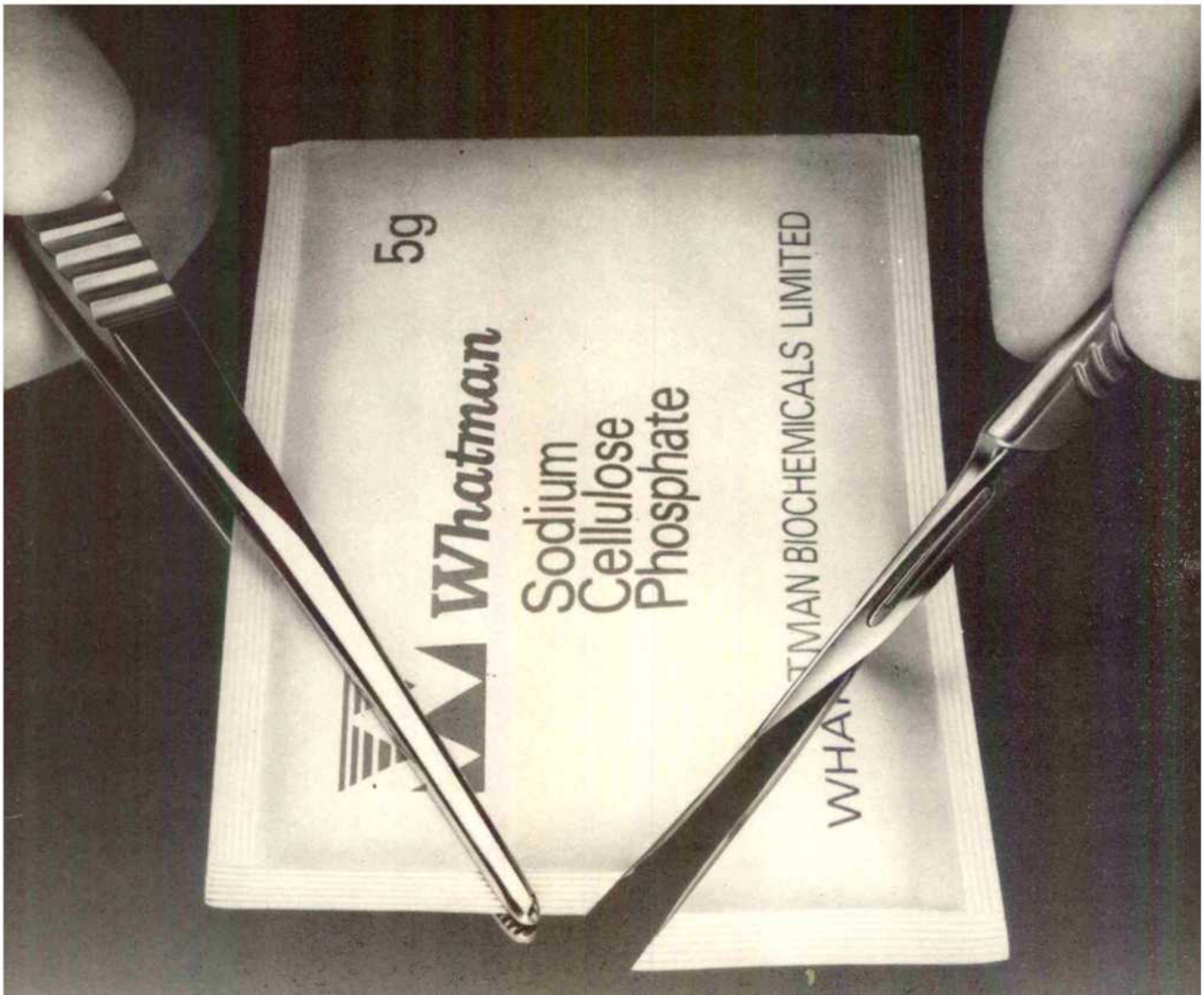

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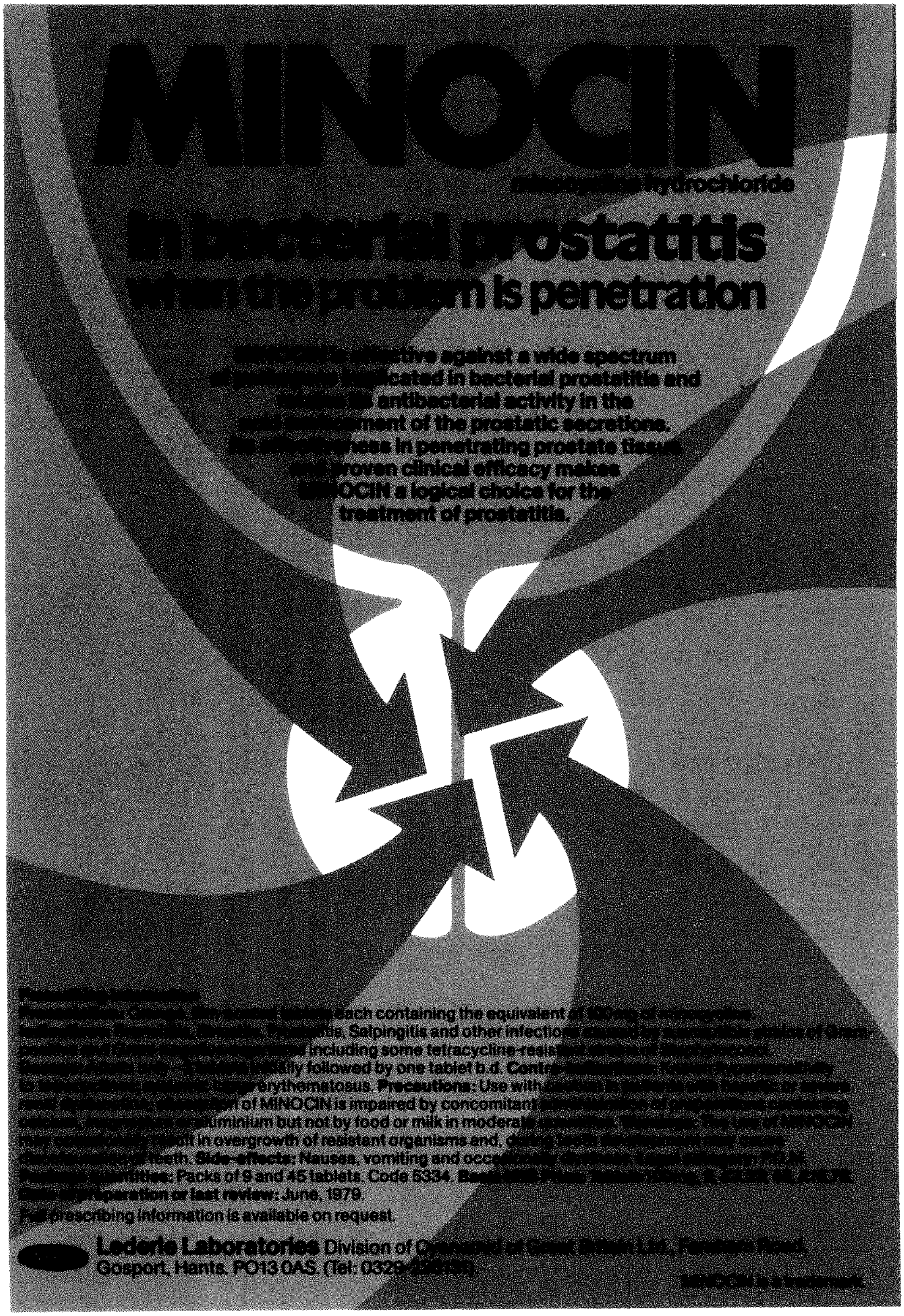

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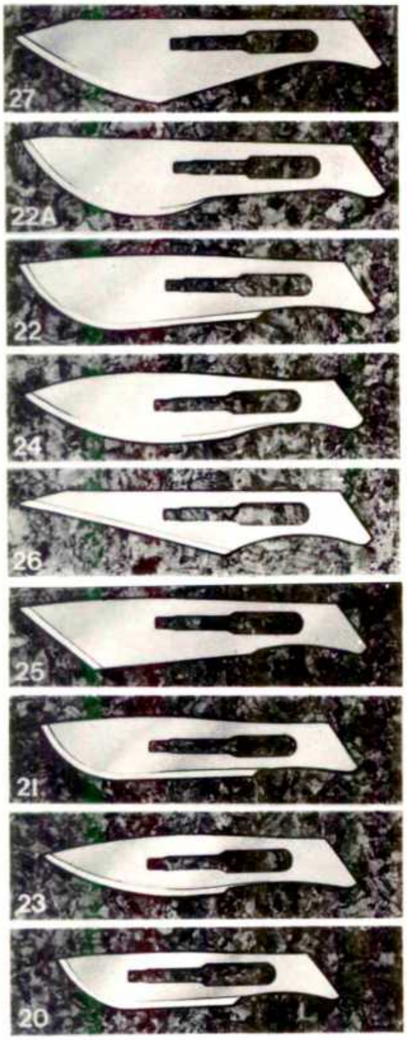

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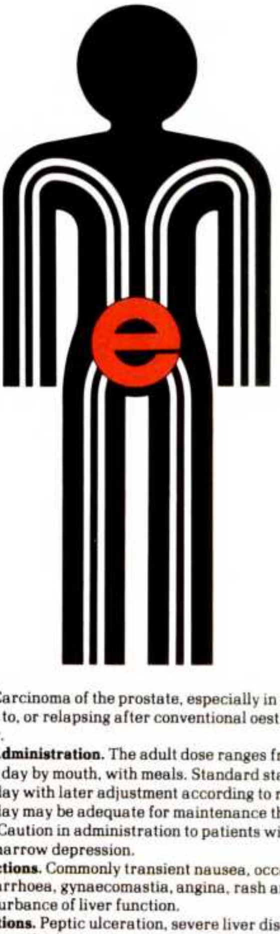

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1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer, E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111; 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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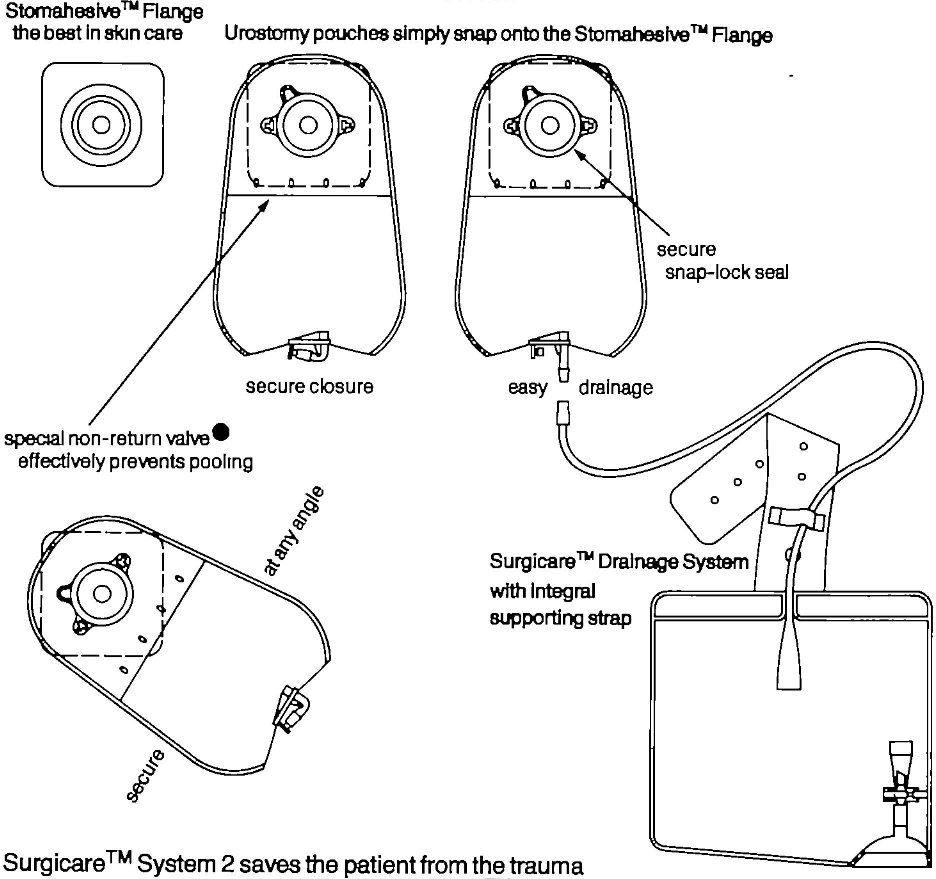

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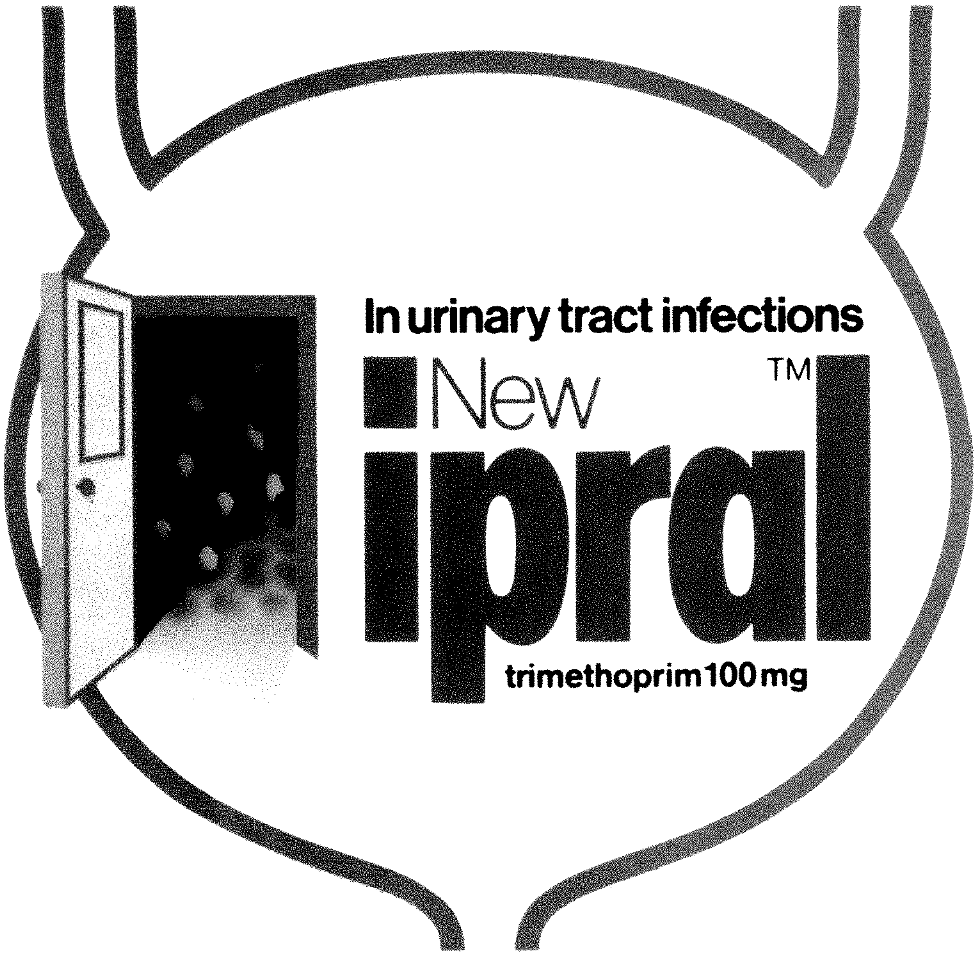

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References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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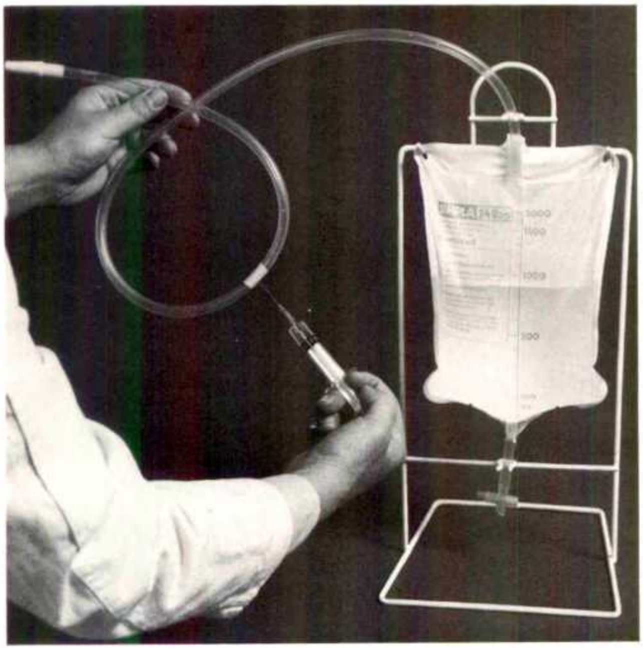

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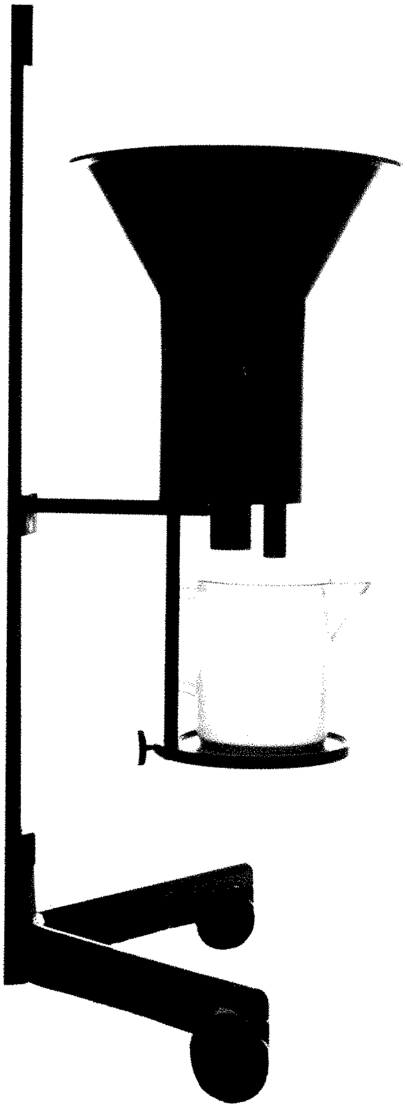

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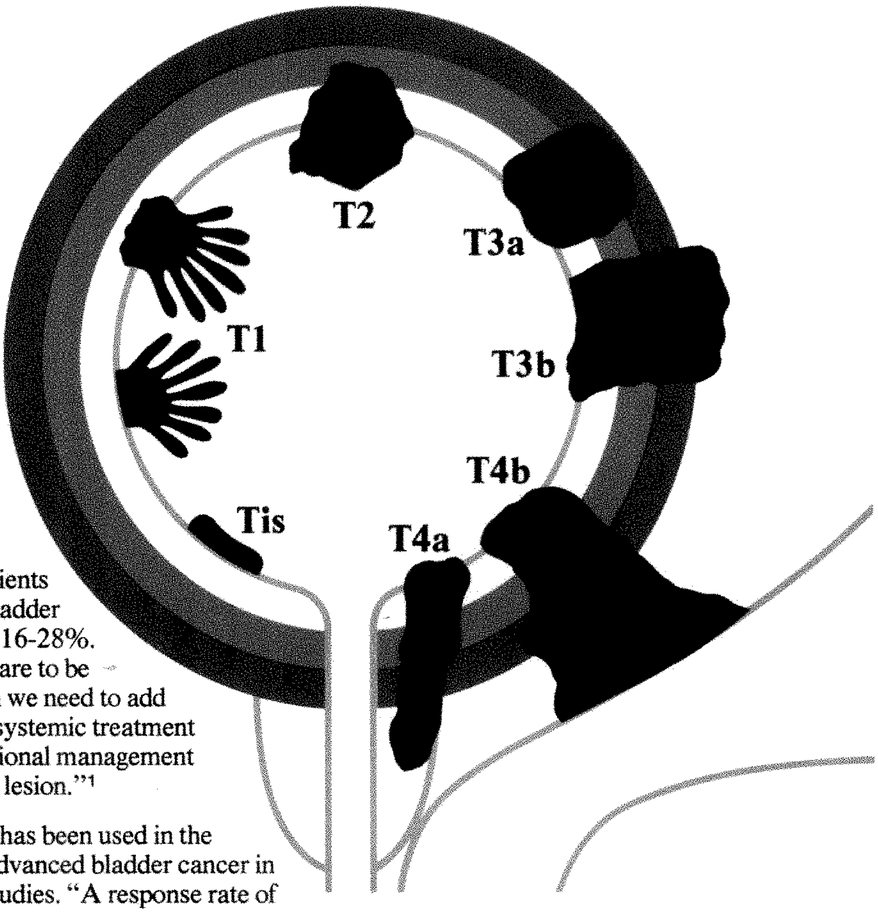

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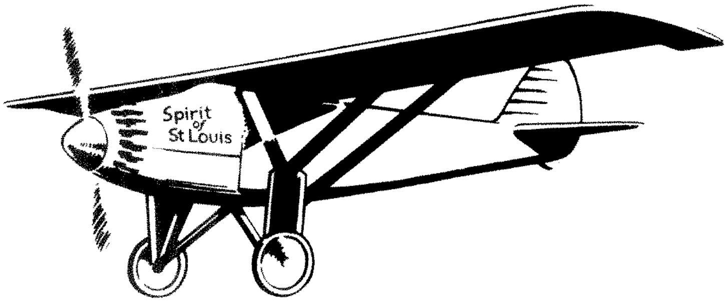

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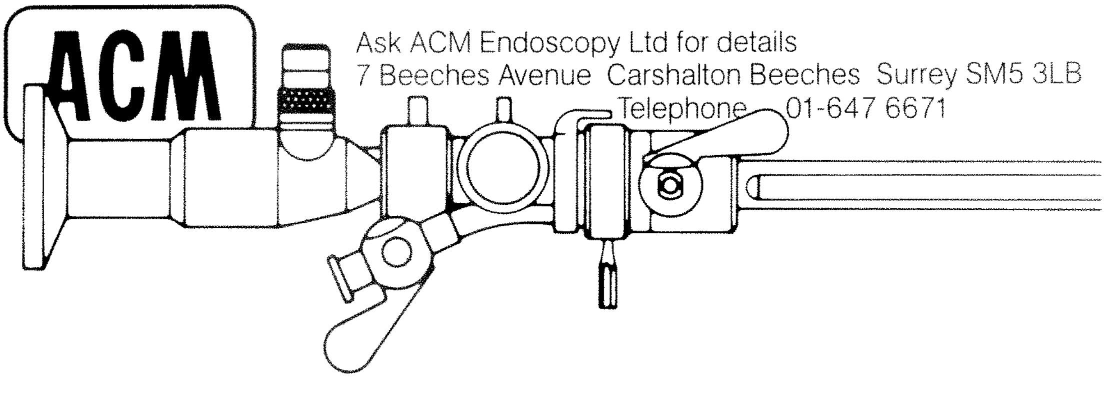

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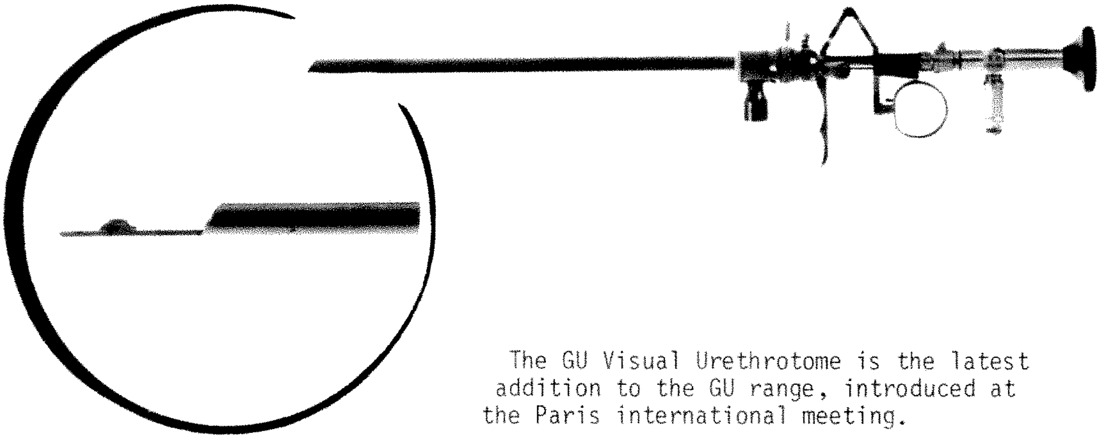

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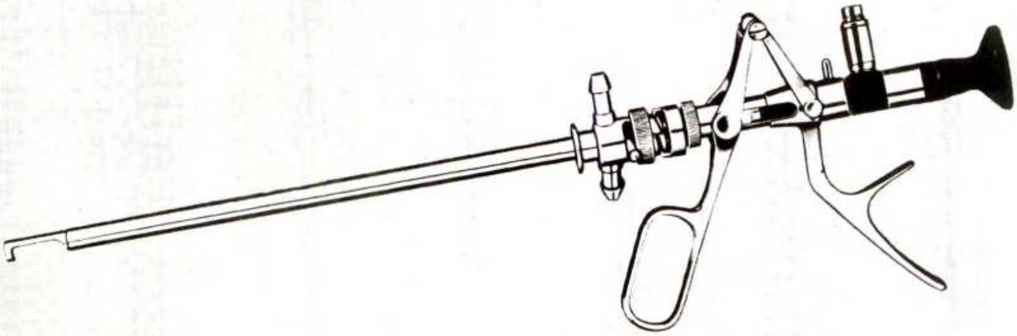

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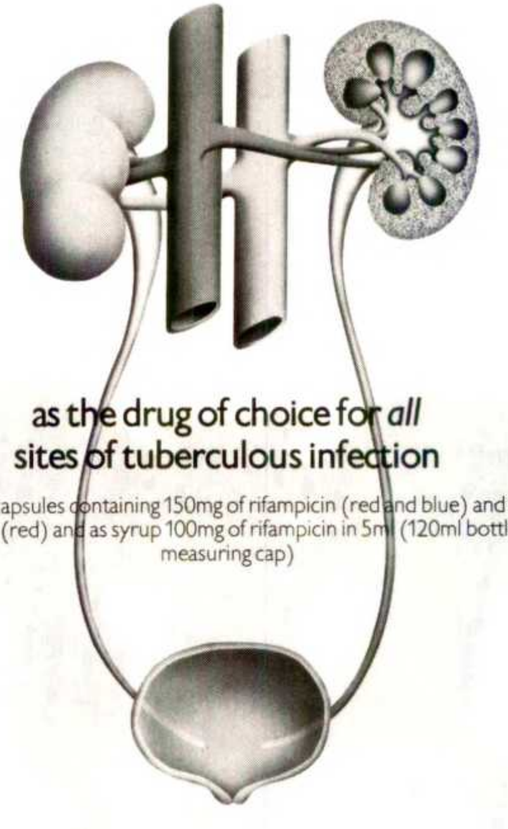

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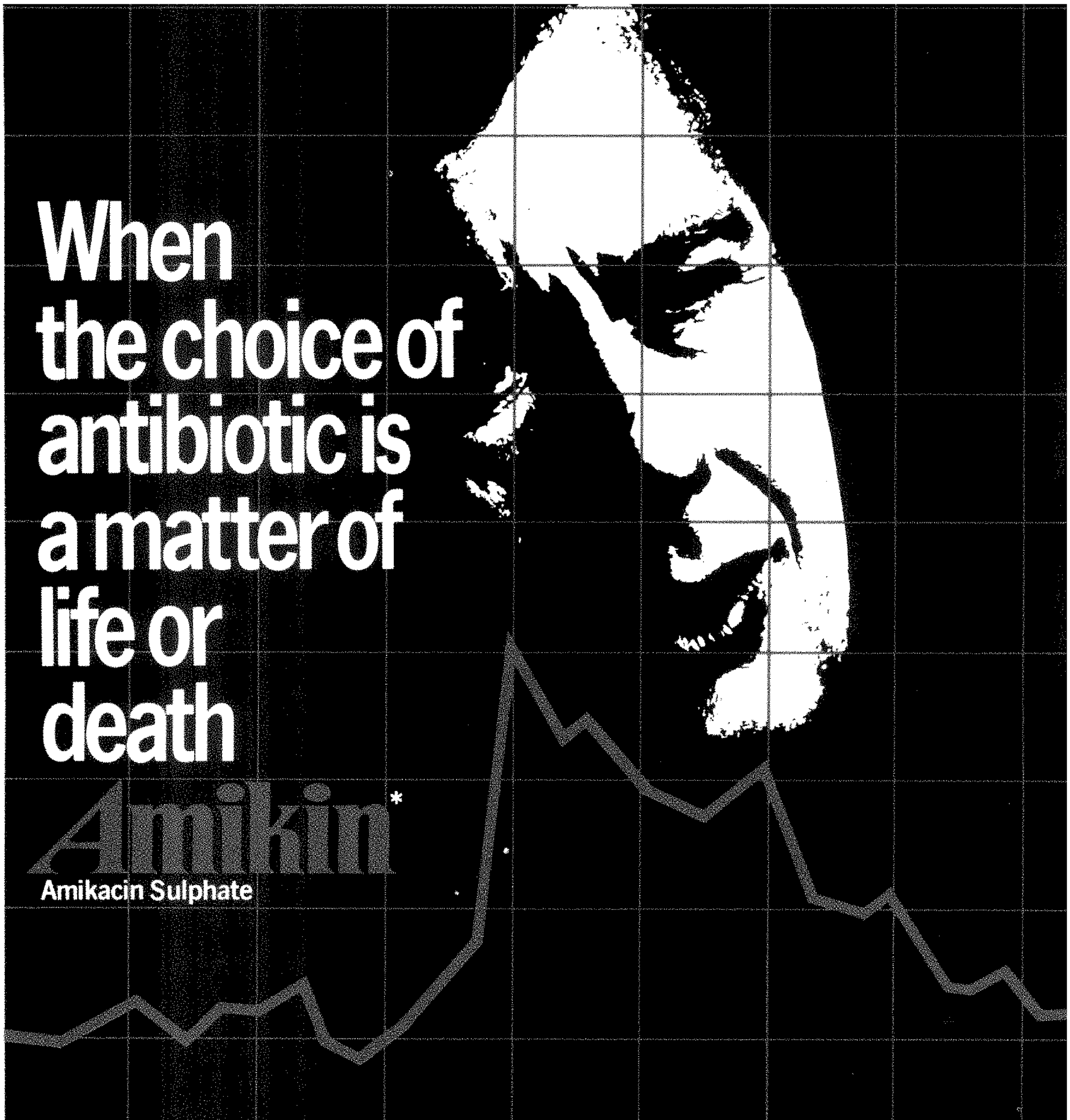
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References:
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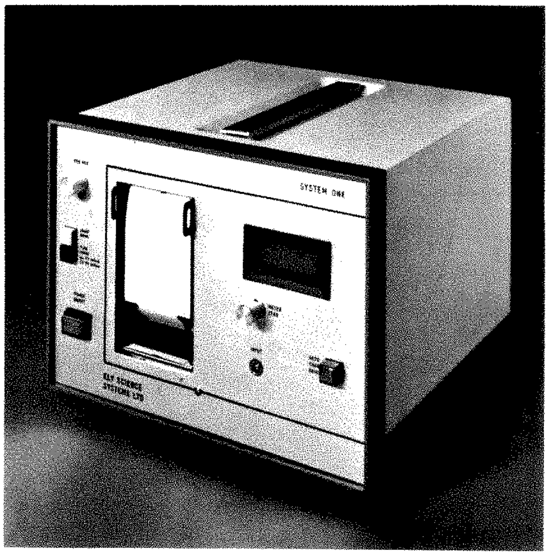

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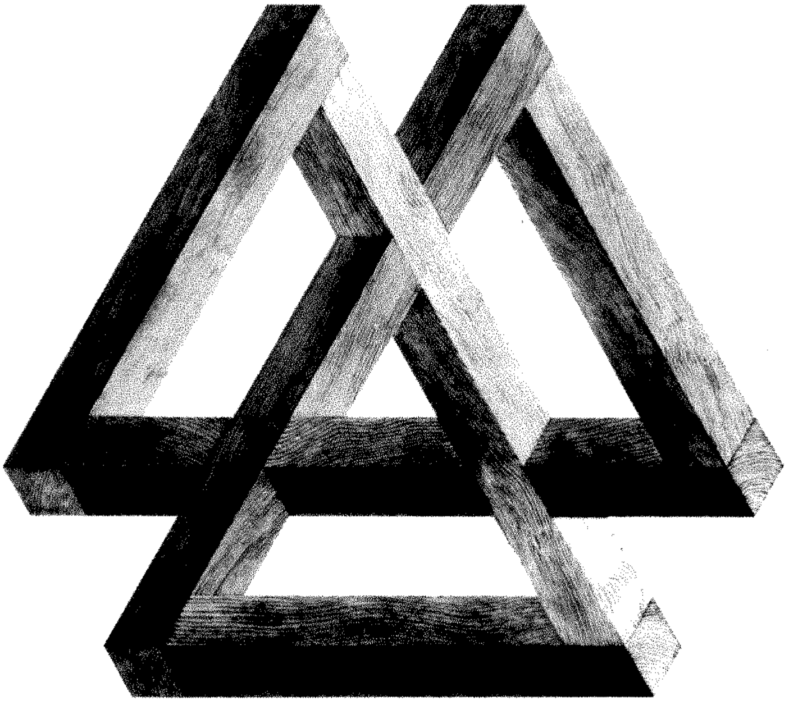

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Hippocrates: Founder and Pioneer of Urology

C. DIMOPOULOS,* A. GIALAS, M. LIKOURINAS, G. ANDROUTSOS and A. KOSTAKOPOULOS

Department of Urology, King Paul's Hospital, Athens, Greece

Hippocrates' contribution to the study of the anatomy and pathology of the urinary tract cannot be denied, although his work has not received the recognition it deserves. It has been said that he delayed the development of surgery (and urology in particular) by condemning the cutting of the bladder for stone; it is now evident, however, that he condemned not the operation but the inexperience of those performing it, and he insisted that it should be done only by those with special knowledge and experience—such people would now be called urological surgeons.

A thorough study of the Greek text of *Corpus Hippocraticum* shows him to be the founder and pioneer of urology in the fifth century BC, for he studied the subject systematically and wrote several treatises on disorders of the urinary tract and related urological conditions. His observations and suggestions concerning the anatomy and physiology of the urinary tract show that his knowledge of urology was accurate and his explanations of the aetiology of some urinary tract diseases surprisingly sound. His theory of renal stone formation and his diagnostic interpretations of the abnormal elements in the urine by macroscopic examination (uroscopy) are still respected. He wrote: "No other system or organ of the human body gives us so much diagnostic information by its excretion as does the urinary tract."

Hippocrates studied many urological disorders. He did not avoid open operation on the kidney and advised his colleagues to operate on patients suffering from pyonephrosis and renal abscesses. Four cases of renal abscess drained by deep loin incision have been described.

Hippocrates was aware of the high mortality rate and the late complications of many urological operations (particularly cystotomy) and wrote: "The injuries and operations of brain, heart, diaphragm, spinal cord, large veins and urinary bladder are the main causes of death." He estimated that as many died from injury to the urinary bladder as from injury to the brain, heart, etc. A similar view was held by the Indian, Sucruta, who lived before Hippocrates and who wrote: "The result of cystotomy is unsafe even though the operation is being performed by a very experi-

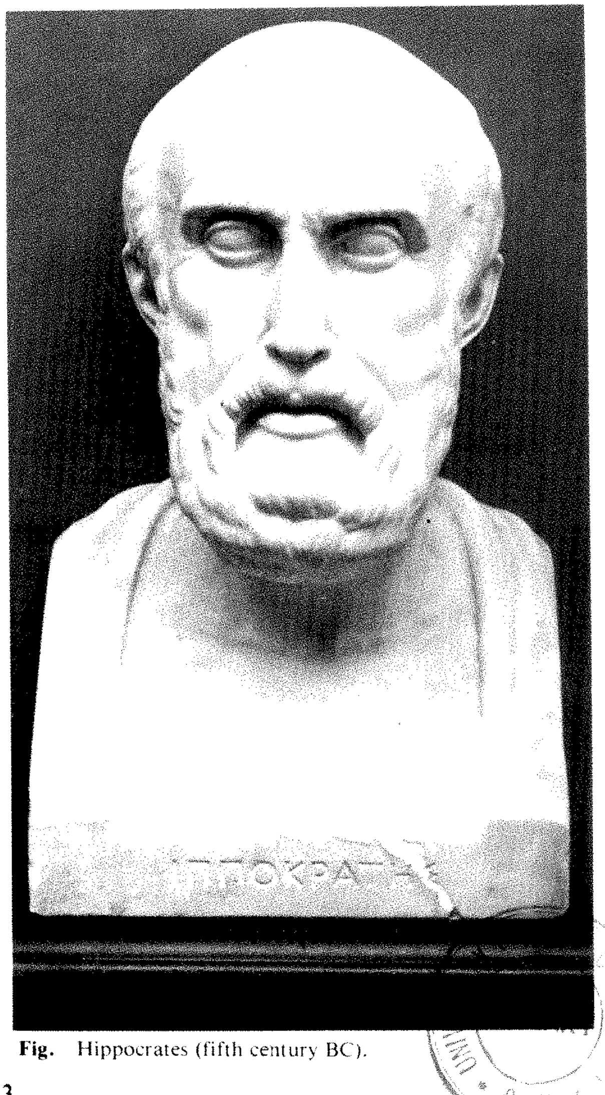

Fig. Hippocrates (fifth century BC).

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* The *British Journal of Urology* is pleased to publish these notes on Hippocrates to mark the occasion of the meeting of the European Association of Urology in Athens in May under the Presidency of Professor Dimopoulos.

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enced man, but it is also certain that death is the final result of the unoperated cases. Because of that late risk a conscientious doctor must try to cystotomise his patients, despite the uncertain results of the operation, but he must first ask Isvara's help. In cases where the patient feels dizzy or bends his head during the operation, the doctor must give up the operation; otherwise the patient will die."

During Hippocrates' life and for many centuries after his death, cystotomy tended to cause severe and permanent disability and even death because it was performed by men practising empirical and speculative surgery. Hippocrates therefore advised doctors to avoid this procedure if possible and to refer those who required it to a specialist (chironactes). In this way he tried to protect patients from charlatans and untrained men and he required of all doctors a knowledge of catheterisation of the bladder. It can thus be claimed that specialisation began at this time. In the fifth century BC Herodotos wrote: "For every disease and each part of the human body there is a special doctor. Thus we have doctors for eyes, teeth, the abdomen and finally doctors for obscure [aphanon] internal diseases."

Hippocrates was also concerned about the complications of cystotomy and reported the leakage of urine through the incision, a complication which he had noted following injury to or surgical incisions on other structures such as the bowel, etc. The most severe complications of cystotomy seemed to be gangrene and necrosis of the testis, which resulted in infertility, impotence and personality disturbances.

Hippocrates taught deontology and disapproved of requests for cystotomy from patients seeking castration. The word "temeo" means "castration" in ancient Greek and those who performed it were known as "Tomie". The ancient Indian doctors feared testicular complications after cystotomy and Sucruta wrote: "During cystotomy the patient becomes infertile and sometimes dies if the spermatic cord is cut."

During the Greek and Roman period surgeons performed many cystotomies successfully and Amonios (third century BC) devised a special instrument known as a lithotome for the operation. The Alexandrian surgeon, Megis, also performed cystotomy and Celsus wrote: "Incision and injury of the urinary bladder may cause death because of the bladder's neural stimulation."

It is thus apparent that Hippocrates, through his research, observations, analyses and experiments, laid the foundations of modern medicine in general and urology in particular; in so doing he furthered the pursuit of happiness which, according to Greek ideology, is the greatest attainment of human society.

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Hydatid Disease of the Genitourinary Tract

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Summary—Seventeen patients were treated surgically for hydatid disease of the genitourinary tract. The diagnosis of echinococcosis was facilitated by a positive Casoni test with evidence suggestive of a cystic tumour following intravenous urography, angiography, ultrasound or renal scan. Barium enemas, cystography and cystoscopy were of great help in cases of lower urinary tract hydatid disease.

Seven patients with hydatid disease of the kidney underwent nephrectomy. The other 6 patients with renal involvement had excision of the cysts only. Treatment of the 4 patients with lower genitourinary tract hydatid disease was on an individual basis. There was no mortality and no significant morbidity.

The first description of hydatid disease in the literature of the Middle East appeared in the book *Al-Hawi* or *Continens* by Al-Rhazes (AD 860-925). The following comment is translated from *The Genuine Works of Hippocrates* (Adams, 1939): "Watery balloons may form in the liver within its investing membrane more often than in other organs. Such balloons may be seen in the high parts of livers of many animals that we slaughter."

The parasitic nature of hydatid disease was apparently not recognised, however, until 1683, when Edward Tyson read a paper on the subject to the Royal Society, identifying the parasites as "worms *sui generis*". Hunter (1835) was the first to formulate the idea that renal cysts gave rise to aseptic rupture. More than 60,000 cases of *Echinococcus* in man have been reported during the last 20 years, of which only 10 were in the lower genitourinary tract (Deklotz, 1976).

Infestation with *Echinococcus* is quite common in Iran, especially in villages where sheep, dogs and man live in close contact with each other, and the management of the various presentations and complications of hydatid disease is an everyday surgical problem. However, hydatid cyst of the genitourinary tract is less common and we report our experience with 17 such cases which were treated surgically.

Patients and Methods

We reviewed all cases of genitourinary echinococcosis recorded in Nemazee and Saadi hospitals of Shiraz University during the period 1954 to 1979. There were 540 admissions to the surgical department for hydatid disease of all organs, including 13 hydatid cysts of the kidney and 4 of the lower urinary tract. Five of these have already been reported (Raffi and Dutz, 1967; Amir-Jahed *et al.*, 1975; Nourmand, 1976). Most of the patients came from rural areas and belonged to the lower income groups of farm hands and labourers.

It should be noted that our study does not include all cases in the province of Fars or even in Shiraz, since a number of patients with hydatid disease were treated in private hospitals whose records were not available to us.

Results of Survey

A. Renal Echinococcosis

The 13 patients with renal echinococcosis (7 male and 6 female) ranged in age from 6 to 65 years with a mean of 29 ± 17. All but one were less than 45 years and the majority (77%) were more than 15 years of age (Table 1).

The duration of symptoms before diagnosis varied from less than one year to more than 4

Table 1 Age Distribution

Age in years	*Number of patients*
1-15	3 (23%)
16-45	9 (69%)
Over 45	1 (7.6%)
Total	13

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 2 Duration of Symptoms in Years

Age in years	< 1	1-2	2-3	3-4	> 4
0-15	3	0	0	0	0
16-45	4	4	1	0	0
Over 45	0	0	0	0	1

years (Table 2). It was difficult to evaluate the duration of the disease with accuracy, but the majority of patients (11) had symptoms lasting from one to 2 years.

Nine patients presented with an abdominal mass. Pain, haematuria and acute crisis were also noted in these patients (Table 3).

The diagnosis was ultimately established by surgical exploration in all patients, but prior to surgery the clinical findings (as shown by a positive Casoni test, intravenous urography, angiography, ultrasound and renal scan) indicated the presence of hydatid disease in 7 patients. The Casoni test was positive in 7 and negative in 6 patients. The eosinophil count, available in 11 patients, was raised in 5. No specific test could be defined as significant in the diagnosis of renal echinococcosis.

Associated cysts of other organs were present in 4 patients, whereas the other 9 harboured cysts of the kidney only. Associated cysts involved the liver in 2 patients and the spleen in one. One patient had cysts in both liver and spleen.

The surgical procedure was facilitated in 6 patients by the superficial location of the cyst or by its adherence to the kidney parenchyma being insignificant enough to allow easy excision. However, excision of the cysts necessitated total nephrectomy in 6 patients and partial nephrectomy in one (Table 4). The cavity remaining after removal of the cyst caused no problem and except for post-operative haematuria, patients with excision of cysts as against those with nephrectomy had no increased morbidity. There was no mortality in this series and there has been no recurrence to date.

Table 3

Clinical presentations	*Number of patients*
Palpable mass	9 (69%)
Abdominal and flank pain	2 (15%)
Haematuria	1 (7.6%)
Acute crisis	1 (7.6%)
Total	13

Table 4 Surgical Treatment of Renal Echinococcosis

Procedure	*Number of patients*
Excision of hydatid cyst	6 (46%)
Total nephrectomy	6 (46%)
Partial nephrectomy	1 (7.6%)

B. Lower Genitourinary Tract Echinococcosis

There were 4 patients with lower genitourinary tract echinococcosis (Table 5); in none was a pre-operative diagnosis made. The main complaints were dysuria, frequency, backache and testicular pain, and clinical examination revealed a mass in each case. Intravenous urography, barium enema and cystoscopy showed gross indentation of the bladder floor with stretching of the trigone. Frozen section showed only chronic inflammation in both the prostatic and bladder hydatid cyst. Treatment varied from partial cystectomy to evacuation of the cyst. There was one recurrence.

Discussion

A. Renal Hydatid Disease

The 5 cases reported previously were cysts without involvement of other organs presenting with a mass in the loin. Three of these could be diagnosed on the basis of the Casoni test. Since then we have had better facilities, including selective renal angiography, ultrasound and renal scan, and they have helped us to diagnose renal hydatid disease with greater accuracy.

Renal function tests were not helpful. Serological reaction for *Echinococcus* was of some help, although this may fail in cases where ruptured cysts have become infected. Eosinophilia is not a specific sign in Iran since most patients in the endemic area suffer from one or other type of intestinal parasitosis.

The presenting symptoms were similar to those

Table 5 Extra-Renal Hydatid Cyst

Age in years	*Anatomical position*	*Symptoms*	*Treatment*
35	Retroperitoneal extending from prostate	Backache, mass	Evacuation of cyst
65	Prostate	Urinary retention	Prostatectomy
25	Epididymis	Testicular pain	Excision
20	Bladder	Frequency, dysuria	Partial cystectomy

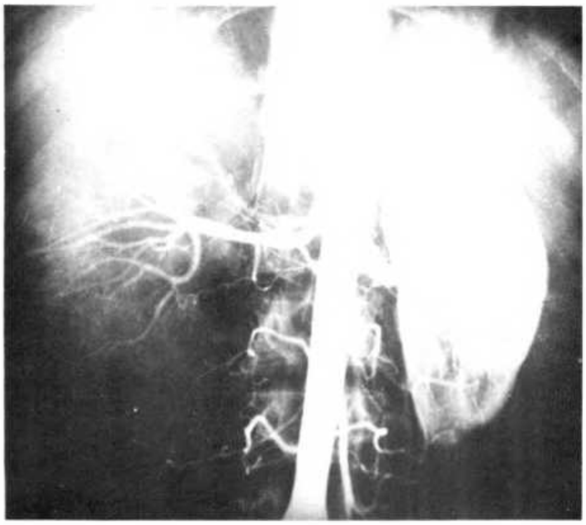

Fig. 1 Angiogram showing distortion of the right kidney by the hydatid cyst.

of a renal cyst or carcinoma and usually consisted of flank pain, a sensation of pressure and distortion of the caliceal systems on X-ray. Occasionally there appeared to be a mass in the lower pole of the kidney. Selective renal angiography was equivocal as it did not give a clear-cut picture of either a solid or a cystic lesion. Figure 1 shows an example and Figure 2 demonstrates the pathological specimen in the same case. However, ultrasonic examination and renal scan helped us to diagnose pre-operatively the nature of the mass in the kidney.

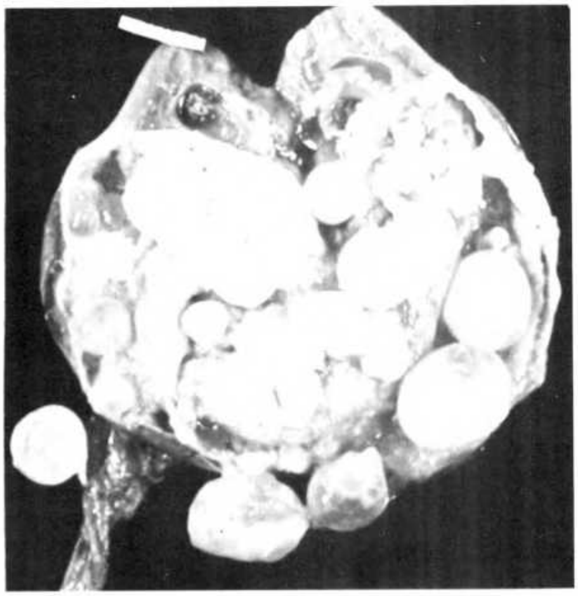

Fig. 2 Nephrectomy specimen of the same kidney as in Figure 1, showing the cystic part and dilated ureter containing daughter cysts.

B. Lower Genitourinary Echinococcosis

Primary echinococcal cyst of the retroperitoneum is rare. For the hydatid embryo to reach the retroperitoneum, it is postulated that it must pass through the portal systems into the liver, retroperitoneal lymphatics or directly via the gastrointestinal tract (Mukherjee *et al.*, 1973).

Diagnosis and treatment can be carried out at the same time, taking care not to spill the contents as this may cause both recurrence, as in one of our cases, and mortality (Ghooi and Sikdar, 1963; Mathur *et al.*, 1969).

In a survey of village tribal communities in Southern Iran (Petrosian *et al.*, 1964), 3.5% of the tribal population showed a positive Casoni test. Moreover, a study of 100 dogs from the streets of Shiraz showed 25 to be infected with *Echinococcus*. Despite this extensive infestation, the present series consists of only a small number of patients who presented over a long period (25 years).

It is noteworthy that in the large number of autopsies in which many hydatid cysts were seen, no asymptomatic small renal hydatid cysts were found; this emphasises the relative rarity of renal involvement.

This study confirms that although echinococcosis is still a major health problem in endemic areas, the disease is rather uncommon in the genitourinary tract and it is associated with low morbidity and mortality. However, it is emphasised that the use of renal cyst puncture under fluoroscopy may carry a high risk in endemic areas, even though there may be a negative Casoni test. This stresses the importance of improving the present serological and immunological tests. False negative tests in up to 37.5% of cases have been reported by Amir-Jahed *et al.* (1975). All of these points emphasise the fact that the diagnostic approach to renal hydatidosis must be based on a composite picture of the clinical as well as the radiological features of the case.

The surgical treatments of choice for hydatid disease range from excising the cyst to total removal of the organ, and should be determined by the size of the lesion, its encroachment upon adjacent structures and the extent of the damage. The choice is usually made at the time of operation. However, it should be stressed that marsupialisation or open drainage in any form, as used to be the practice, is not recommended under any circumstances (Saidi, 1976).

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Compensated Obstruction of the Renal Pelvis

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Summary—Three children with equivocal pelviureteric junction obstruction are described. The renal pelves were only slightly dilated and emptied well with posture change or diuresis, but there was disproportionate dilatation of the calices. On direct puncture perfusion of the pelvis there were repeated high pressure contractions which resulted in emptying, but basal pressures remained normal. This condition appears to be analogous to the partially obstructed but compensated bladder.

The measurement of perfusion pressure is a valuable, though invasive test of obstruction of the upper urinary tract (Whitaker, 1973). In the course of investigating children with equivocal pelviureteric junction obstruction by this method, a small group of patients has been recognised in whom the renal pelvis emptied by unusually vigorous contraction. On intravenous urography, the size of the renal pelvis was relatively normal, but there was disproportionate dilatation of the calices.

Patients

Case 1

A 2-year-old boy investigated for urinary tract infection was found to have a solitary left kidney with markedly dilated calices. On the 10-min intravenous urogram (IVU) film (Fig. 1) the renal pelvis was filled but not distended. The ureter was not seen. Fifteen minutes after intravenous frusemide, all contrast had left the pelvis and was seen in the bladder (Fig. 2). The kidney was explored and perfused. At 9 ml/min there was a rapid rise in pressure with vigorous contractions reaching 100 cm H_2O (Fig. 3). The pelvis was seen to empty periodically, following which the pressure temporarily returned to normal. Pyeloplasty was performed.

Case 2

A 10-year-old boy had an IVU for an episode of haematuria (Fig. 4). The calices of the right kidney were markedly distended and the parenchyma thin. The pelvis was not enlarged and contrast medium was seen in the ureter. On standing, the pelvis had almost com-

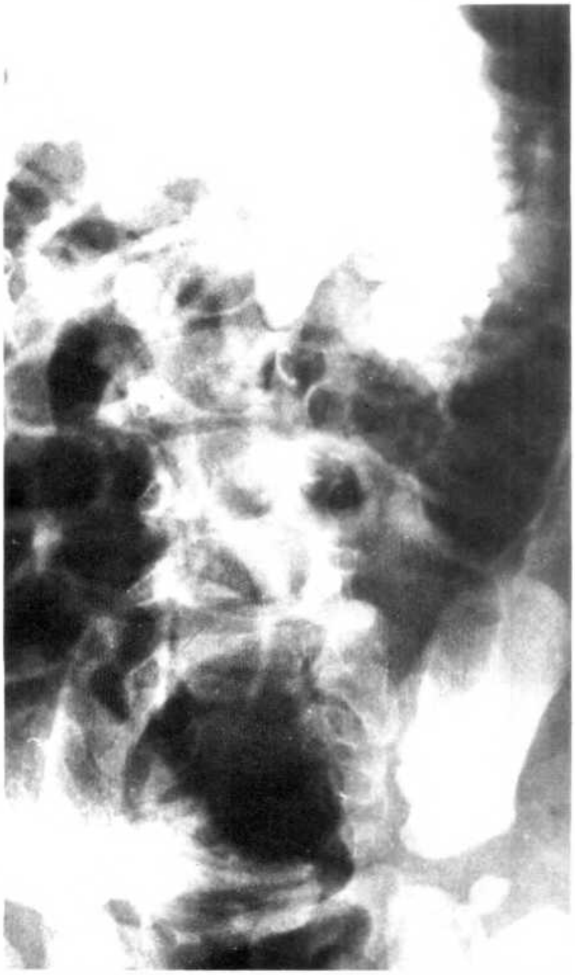

Fig. 1 Patient 1. IVU 20 min: caliceal dilatation disproportionate to that of renal pelvis.

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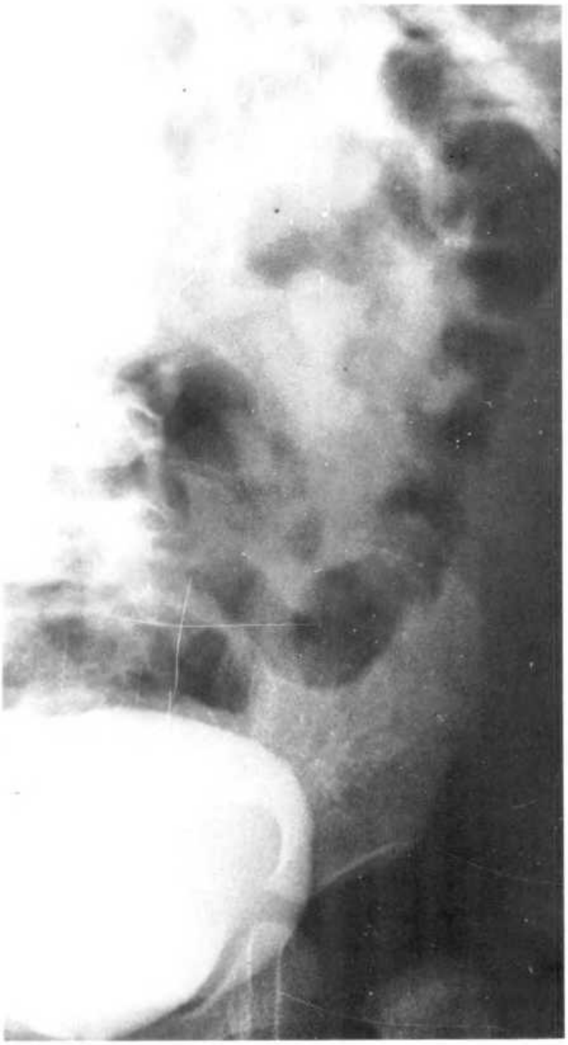

Fig. 2 Patient 1. IVU 15 min after intravenous frusemide: all contrast has passed from renal pelvis to bladder.

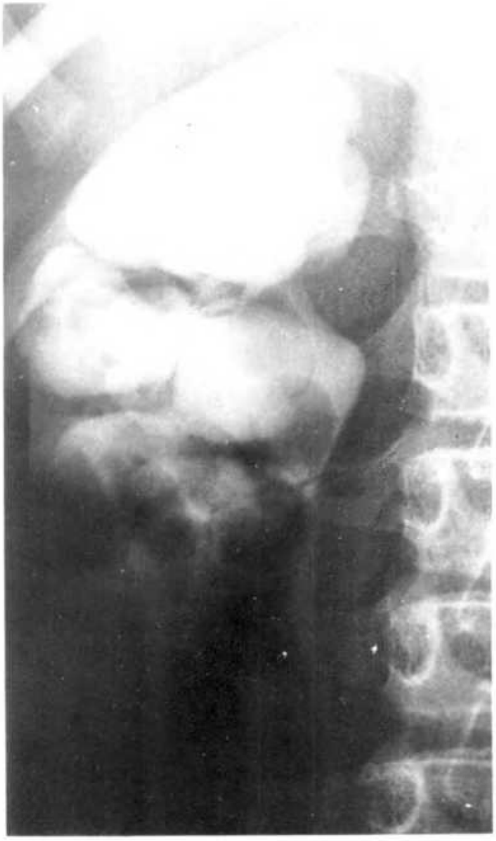

Fig. 4 Patient 2. IVU 10 min: caliceal dilatation disproportionate to that of renal pelvis. Contrast in ureter.

pletely emptied (Fig. 5). Perfusing at 3.5 ml/min produced vigorous contractions, but the basal pressure remained below 15 cm H_2O for the 20 min of the study (Fig. 6). At 9 ml/min, contractions subsided and the basal pressure rose progressively. Pyeloplasty was performed.

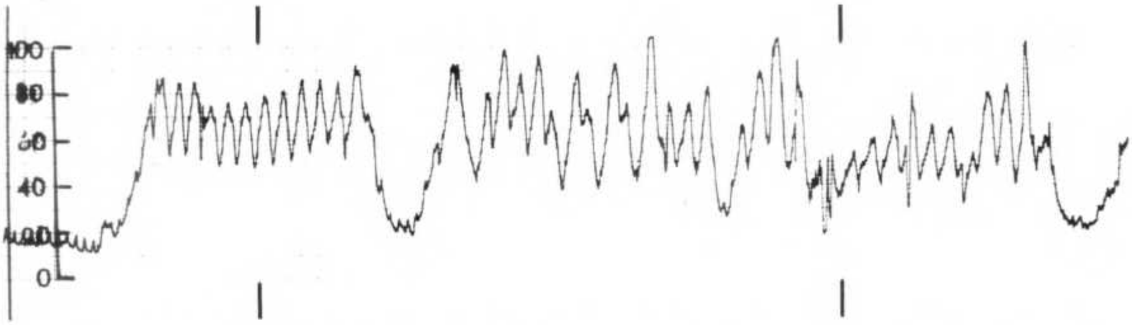

Fig. 3 Patient 1. Pressure trace during perfusion at 9 ml/min: basal pressure intermittently returns to normal after periods of vigorous contraction, observed to correspond to intermittent emptying of the renal pelvis. Vertical scale: pressure in cm H_2O. Horizontal scale: time 200 s between broken vertical lines.

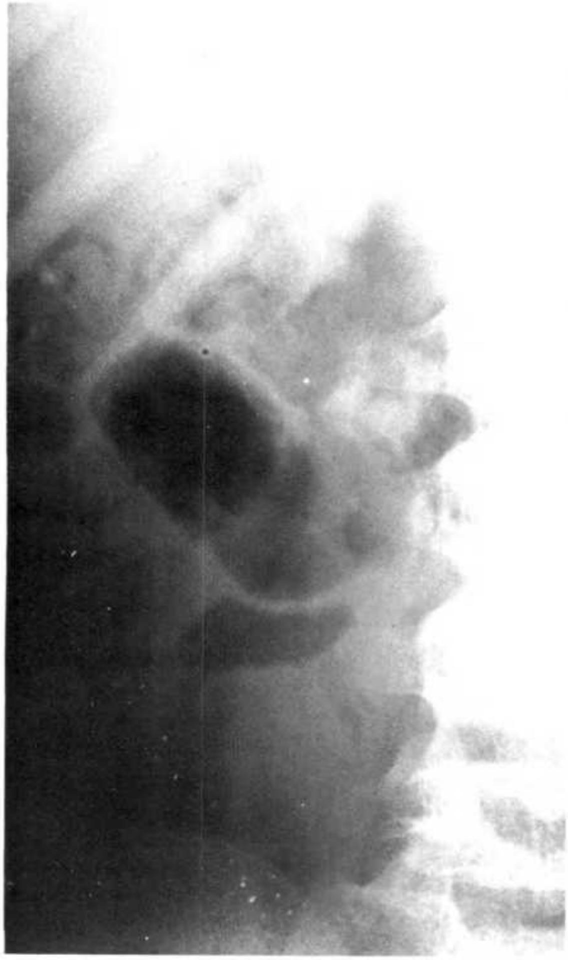

Fig. 5 Patient 2. IVU 40 min (after standing): only a trace of contrast remains in the renal pelvis.

Case 3

A 12-year-old boy with a family history of tuberculosis had an IVU for a persistently raised ESR. The calices of the right kidney were dilated and there was a suggestion of pelviureteric junction obstruction (Fig. 7). On standing, however, the pelvis drained almost completely (Fig. 8). On perfusion at 3.5 ml/min, basal pressure remained at 20 cm H_2O but there were vigorous contractions reaching 60 cm H_2O which emptied the pelvis. More rapid perfusion produced a sustained rise in the basal pressure. Pyeloplasty was performed.

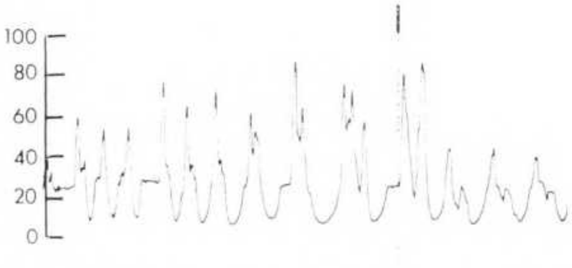

Fig. 6 Patient 2. Pressure trace during perfusion at 3.5 ml/min: sustained high peak pressures. Basal pressure remains normal. (Calibration same as Fig. 3.)

Discussion

In the 3 patients reported here, there was neither an extrinsic nor an intraluminal abnormality, so that these patients are considered to have had examples of primary or idiopathic pelviureteric junction obstruction.

The maximum pressure generated by a contraction wave of the normal renal pelvis in children was found by Edmond to be 12 cm H_2O (Edmond *et al.*, 1970). During perfusion of the obstructed renal pelvis there is a rise in the basal pressure

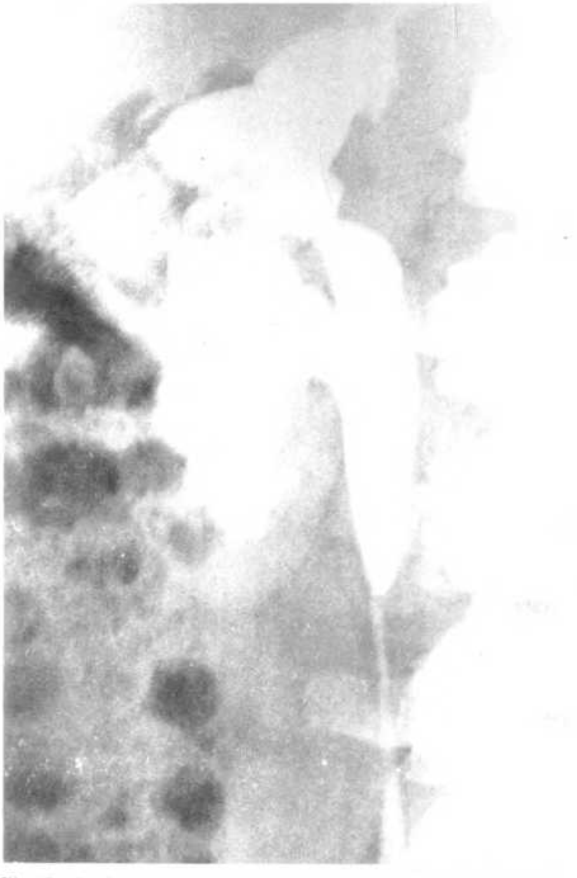

Fig. 7 Patient 3. IVU 10 min: full renal pelvis and calices. Narrowing at pelviureteric junction with contrast in ureter.

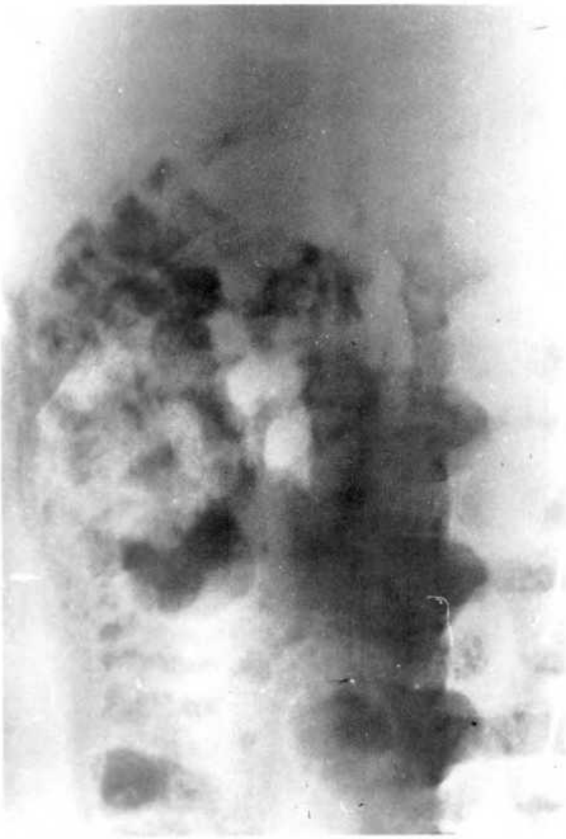

Fig. 8 Patient 3. IVU 45 min (after standing). Good drainage of contrast from renal pelvis.

(Whitaker, 1976). Johnston (1969) found that the amplitude of contractions in pelviureteric junction obstruction in children did not exceed 15 cm H_2O. Michaelson (1974) has récorded pelvic contractions reaching a pressure of 91 cm H_2O during an episode of colic, but sustained high pressure contractions of the renal pelvis with resultant emptying have not been previously described.

The behaviour of the renal pelvis in this group of patients appears to be analogous to the high voiding pressures in the partially obstructed but compensated bladder. The muscle of the pelvis retains its tone and hence contour on the intravenous urogram, but the repeated high peak pressures result in progressive dilatation of the less muscular calices. This may be a mechanism for the urographic appearance described as megacalicosis.

Pelvicaliceal planimetry with frusemide (Whitfield *et al.*, 1977) and diuresis renography (O'Reilly *et al.*, 1978) would not have detected obstruction in these patients. It is not known whether gamma camera renography with deconvolution analysis of cortical activity (Whitfield *et al.*, 1978) could have detected this compensated form of obstruction. As the definition of obstruction ultimately depends on pressure-flow relationships, it seems probable that there will continue to be a place for their direct measurement.

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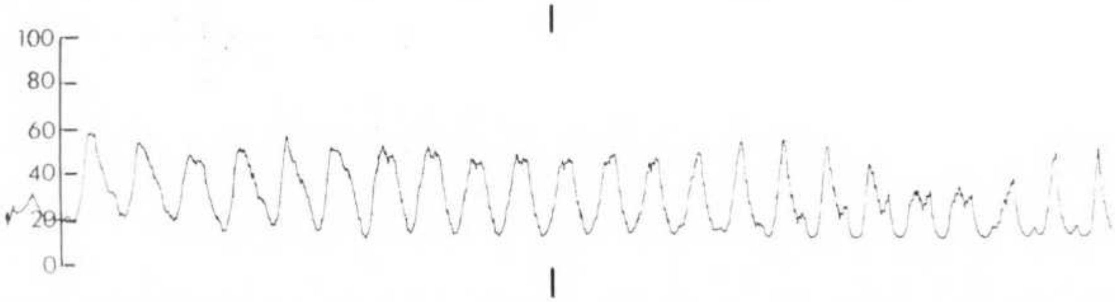

Fig. 9 Patient 3. Pressure trace during perfusion at 3.5 ml/min. Sustained peak pressures of 40 cm H_2O. Basal pressure normal. (Calibration same as Fig. 3.)

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Radical Nephrectomy—an Assessment of Morbidity, Local Control of Disease and its Effect on Prognosis

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Summary—Radical nephrectomy has a morbidity and mortality similar to that of the more simple procedure. Local control of disease may be obtained safely even in those patients with gross venous extension and worthwhile survival may be obtained in this group of patients. Further study of this extended operation would appear desirable.

Diagnosis of a renal mass lesion can now be carried out radiologically with an accuracy approaching 100%. Surgery for carcinoma may be performed without the need to "explore the kidney" and confirm the diagnosis. The urologist has been able to take advantage of this and plan his procedure in the light of the radiological estimate of the extent of the disease.

Robson *et al.* (1969) suggested that carrying out a "radical nephrectomy", *i.e.* removing the kidney within the intact perirenal (Gerota's) fascia, together with the adrenal *en bloc*, improved the prognosis. Skinner *et al.* (1972) reported similar encouraging results.

The term "radical", in surgery, is somewhat emotive and to many surgeons suggests an extensive mutilating procedure, with a heavy cost to the patient. It is important to know what added morbidity and/or mortality are associated with such a procedure, and to compare them with the benefits gained. For these reasons we have carried out an assessment of the operation of radical nephrectomy in terms of:

(*a*) Post-operative morbidity and/or mortality compared with a similar number of patients undergoing simple nephrectomy.
(*b*) Local control of disease.
(*c*) Prognosis related to local control.

Technique of Radical Nephrectomy

The operation is carried out via a thoracoabdominal approach through the ninth or tenth intercostal space. The abdominal extension of the incision is continued in the line of, or just above, the umbilicus as far as the rectus muscle; the latter may be divided if greater exposure is required. The diaphragm is detached circumferentially and the peritoneal cavity is entered. On the right side the subphrenic space is entered in the plane between perinephric fascia and the diaphragm, after which the peritoneum is divided along the lower margin of the liver, the adrenal vein divided and the adrenal displaced inferiorly. The inferior vena cava is then followed inferiorly, displacing the duodenum and right hepatic flexure. The renal artery may be ligated in continuity between the aorta and cava or as it emerges from beneath the inferior vena cava and the vein is then divided. Inferiorly the perinephric fascia blends with the mesentery of the colon and retroperitoneal fat, and unnamed veins running in this area, and the spermatic vein should be controlled. The ureter is divided at the pelvic brim.

The dissection differs on the left side in that the left colon is mobilised from the superior aspect of the perinephric fascia, the lienorenal fold is entered, and the middle and superior adrenal veins ligated. In the latter part of the series the arteries have been controlled by Gianturco coils pre-operatively.

Post-operatively, the chest is drained for 24 h, the wound area by Redivac suction also for 24 h.

Material

Radical nephrectomy as described above has been carried out on 22 patients with carcinoma in the years 1974 to 1978. This group of patients has been compared with regard to morbidity and mortality with 22 patients undergoing standard nephrectomy for a variety of conditions during the same period.

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Table 1 Age, Date and Side of Operation in Nephrectomy Patients

	Radical nephrectomy			*Simple nephrectomy*		
	Number	*Mean age*	*Age range*	*Number*	*Mean age*	*Age range*
Males	11	61 years	49-72 years	8	55 years	22-74 years
Females	11	57 years	28-67 years	14	65 years	39-82 years
	Number	*Right*	*Left*	*Number*	*Right*	*Left*
Males	11	6	5	8	3	5
Females	11	8	3	14	4	10

Results

Table 1 shows the age and the sex distribution of the 2 groups. Twenty-one of the 22 radical nephrectomies were carried out in the hope of cure, one for palliation. Table 2 lists the indications for simple nephrectomy in the control group.

Morbidity and Mortality

There were no post-operative deaths in either group. Patients who had undergone radical nephrectomy spent on average 10.5 days in hospital (range 7-18 days), compared with 10 days in the control (simple nephrectomy) group (range 7-16 days).

Table 3 shows the post-operative complications. Post-operative urinary retention was a common problem in both groups and was not confined to males only. One patient in the radical group required immediate reoperation because of reactionary haemorrhage: there was no difference in the rate of chest infection or deep venous thrombosis: there were no cases of prolonged post-operative ileus, all being on full fluids by the fifth post-operative day, the majority by the third day.

Control of Disease

The stage of the renal carcinoma was classified as described by Robson *et al.* (1969): 10 patients were Stage I, 3 were placed within Stage II and 9 were found to be in Stage III or IV (Table 4).

Patients in Stages I and II presented no technical problems. Stage III disease required a wide exposure to ensure limited handling of the tumour and ready access to renal veins and vena cava. Of the 8 patients in Stage III, 6 had involvement of the main renal vein and/or vena cava and 2 had lymph node involvement alone (Figs. 1, 2). Where the tumour had major vein extension, the vein was circumferentially detached from the cava between vascular side clamps. Four patients had gross intracaval extension, including one patient with extension to the level of the diaphragm. It was possible to remove the tumour in all cases. Two patients had complete occlusion of the vena cava at the level of the renal veins, but there was no proximal (caudal) caval tumour despite clot extending towards the iliac veins. There was no added morbidity when the cava was opened compared with the 14 patients who underwent simple renal vein ligation.

Survival Following Radical Nephrectomy

Prognosis in renal cell carcinoma is so variable that valid conclusions require prolonged follow-up and significant numbers. Worthy of note, however, is the safety with which the large tumours, or those with major venous extension,

Table 2 Aetiological Factors Leading to Simple Nephrectomy

Staghorn calculus	8
Hydronephrosis with or without stone	4
Pyonephrosis	3
Transitional cell carcinoma (palliative)	3
Renal cell carcinoma (palliative)	2
Infarcted kidney	1
Tuberculosis	1

Table 3 Early Complications Following Radical and Simple Nephrectomy

Radical nephrectomy		*Simple nephrectomy*	
Pulmonary embolus—femoral vein thrombectomy	1	Deep venous thrombosis	1
Chest infection requiring antibiotics	2	Chest infection	1
Reactionary haemorrhage	1	Haematemesis	1
Retention of urine	2	Retention of urine	4

Table 4 Survival and Metastatic Disease

	Number	*Mean*	*Range*	*Metastases*	*Dead*
Stage I	10	33 months	9-49 months	2	1
Stage II	3	33 months	6-51 months	1	1
Stage III	8	18 months	6-36 months	4	3
Stage IV	1	6 months	6 months	1	1

may be removed. Of the 13 patients in Stages I and II, 3 have so far developed metastases and the average survival time to date is 33 months. There has been no local recurrence. Table 5 shows the survival time of patients in Stage III; 50% have developed distant metastases, 6 to 36 months post-operatively.

Discussion

The advantages of a thoracoabdominal approach were described by Chute *et al.* (1949) and Mortenson (1948). Morbidity following this approach has been minimal in all series. Atelectasis and chest infection have been uncommon. Post-operative reactionary haemorrhage is a potential hazard because of the extensive retroperitoneal dissection, but only one patient in the current series required re-exploration for bleeding. There was no morbidity associated with opening or resecting parts of the vena cava. Despite the extensive nature of the dissection, both intraperitoneal and extraperitoneal, with no attempt to close the peritoneum, there were no cases of prolonged ileus. The generous incision allowed control of the vascular pedicle with minimal handling of the tumour. There were no deaths in this small series: Robson *et al.* (1969) reported a

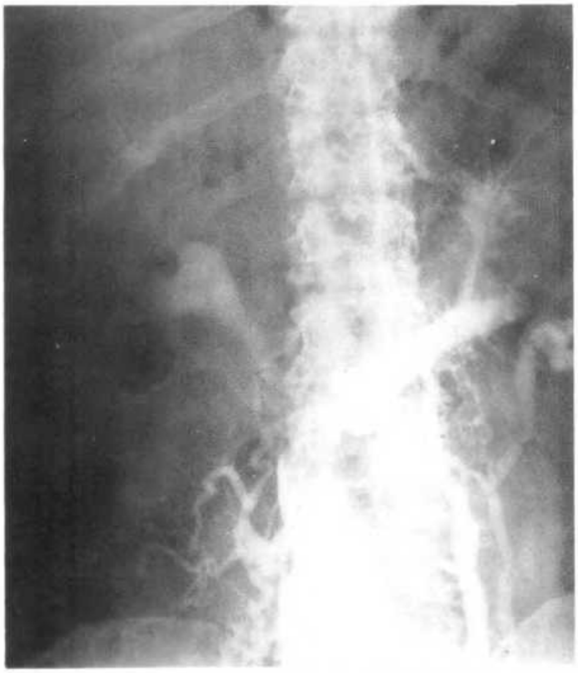

Fig. 1 Inferior cavogram shows complete occlusion of the inferior renal vein and right renal vein from tumour.

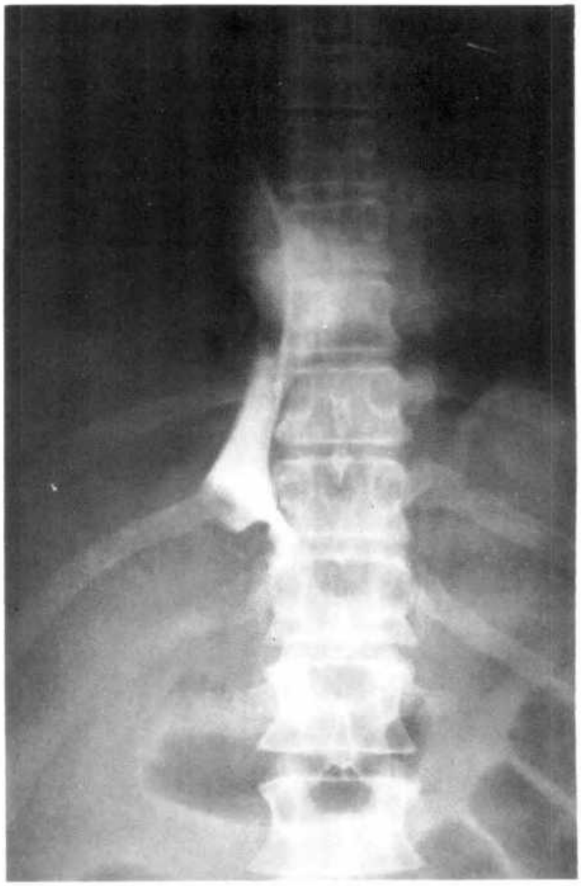

Fig. 2 Extent of obstruction of the inferior cava in the same patient as in Figure 1 is shown by this superior approach to the upper inferior vena cava.

Table 5 Stage III Survival

	Number	*Mean*	*Range*	*Metastases*	*Dead*
Renal vein	2	17 months	14-23 months	1	1
Renal vein and inferior vena cava	3	21 months	6-36 months	1	1
Inferior vena cava and lymphatics	1	27 months	27 months	1	0
Lymphatics only	2	11 months	6-16 months	1	1

3.3% mortality and Scheft *et al.* (1978), reporting exclusively on patients with caval extension of tumour, recorded one death in 12 patients with Stage III disease extending to the vena cava but without distant metastases. An overall 14% mortality was recorded in those with metastases and caval extension in the same series.

The thoracoabdominal approach permits safe clearance of lymph nodes from the aortic bifurcation to the crus of the diaphragm (Robson *et al.*, 1969). In 18 of the patients in whom lymph nodes were removed from the renal bed, renal pedicle and para-aortic and paracaval chains, and were submitted for separate histological examination, 3 only were shown to have tumour involvement. Of these one has died, one has further metastatic spread and the third is free from tumour 16 months after nephrectomy.

In this series to date there has been no evidence of local recurrence or wound implantation. One patient in Stage I has developed chest metastases and died, compared with almost 50% of Stage III patients. Two of 3 patients in Stage III with vein and/or lymph node involvement have developed metastases. This supports the finding of Riches (1963) with relation to the deteriorating prognosis with vein involvement, though Skinner *et al.* (1972) suggested that this was not necessarily so following the radical operation.

In this small group the average survival in Stage III is 19 months, 4 patients having metastases and 3 having died. The most severely affected patient lived 36 months. Scheft *et al.* (1978) reported a 50% survival in a similar group at 31 months with one 12-year survivor. It is therefore important to note that worthwhile long-term survival can be obtained. The part histological grade plays with regard to survival will be reported separately.

Acknowledgement

We should like to thank Mrs Christine Kennedy for typing this manuscript.

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Adult Enuresis—a Symptomatic and Urodynamic Assessment

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Summary—Sixty-five patients (33 females and 32 males) with adult enuresis have been assessed cystometrically.

Patients with primary enuresis may have either nocturnal enuresis alone or diurnal symptoms as well. Abnormal cystometric patterns were found in a high percentage of both types of enuresis. There was a significant correlation between the presence of diurnal symptoms and bladder instability and between nocturia and instability.

Primary enuresis persisting beyond the age of 15 years is commoner than is generally realised. The incidence has been reported as 2% in a longitudinal survey of 847 children (Miller *et al.*, 1973) and 1.2% of 1000 draftees (Levine, 1943). A surprisingly large number of patients do not seek medical help during childhood and those that do are frequently dissatisfied with anything less than a complete cure. It is unfortunate that when the patient attends a clinic for adult enuresis, the treatment regimes are invariably the same as those prescribed for children and again frequently unsuccessful, partly because we do not understand the pathophysiological processes involved.

Investigations may identify the bladder dysfunction which causes enuresis. Cystometric assessment may identify a small bladder, a sensory deficiency or detrusor overactivity. Electromyography performed during cystometry may identify detrusor sphincter dyssynergia and electroencephalographic recordings made during sleep may also be helpful. However, these investigations are invasive and some physicians hesitate to subject all of their patients to such tests and refer only those resistant to treatment.

With a view to gaining a clearer understanding of the natural history, symptomatology and pathophysiology of persistent primary adult enuresis, we have assessed 67 of these patients by cystometry.

Nocturnal enuresis is defined as a normal reflex act of micturition without organic pathology which has produced incontinence at night at least once per month throughout life. If diurnal symptoms of frequency, urgency or urge incontinence also occur, the term "enuretic syndrome" is used (Yeates, 1973).

Patients and Methods

Sixty-five consecutive patients aged 15 and over, referred for treatment of nocturnal enuresis, were assessed by history, physical examination and cystometry.

Cystometry was performed by recording the bladder and rectal pressures, the subtracted pressure and urinary flow rate on a 4-channel Watanabe chart recorder. Filling cystometry was performed in the supine position through an 8 FG catheter infusing normal saline at 37°C at 100 ml/min. A Watson-Marlow infusion pump was used. Voiding pressures were recorded by a 16 FG epidural cannula with the rectal pressure line *in situ*.

Results

Of the 65 patients, 13 were primary nocturnal enuretics, 36 had the primary enuretic syndrome and 16 were recurrent enuretics.

Age/Sex Relationship

The majority of patients were under 30 years of age, there being an apparent regression of enuresis until then. After the age of 30 there was no further regression, although the numbers were small

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Table 1 Age/Sex

	15-20	*21-25*	*26-30*	*31-35*	*36-40*	*41+*
Male	11	10	7	1	1	2
Female	14	6	7	2	2	2
Total	25	16	14	3	3	4

(Table 1). Most of the primary nocturnal enuretics were under 25, whilst most of the recurrent enuretics were over 25.

Nocturnal Enuresis and Nocturia

The number of nights wet in each individual was assessed for the month prior to referral (Table 2). Six of the primary enuretics, 18 of those with the enuretic syndrome and 3 of the recurrent enuretics were wet 6 and 7 nights per week.

Nocturia occurred regularly in 26% of patients, but occurred twice in only 11%. Seventy-five per cent described themselves as deep sleepers. There was no sex bias.

Diurnal Symptoms

Diurnal symptoms were present in 77% of the recurrent enuretics and in 74% of the primary enuretics. Frequency of micturition (less than 2-hourly) was the most common diurnal symptom and occurred in 57%. Urgency of micturition occurred in 48% of cases. Of the 12 patients with severe urgency 9 were females. Urge incontinence occurring every day was experienced by 8 patients (7 females and 1 male). However, 43% of all patients were regularly incontinent.

Cystometry

Sixty-eight per cent of patients had abnormal cystometrograms, results similar to those of Torrens and Collins (1975) who found abnormal cystometrograms in 70% of their cases. Three patterns were found (Table 3):

1. A non-contractile hypertonic bladder with a pressure higher than 15 cm of water at capacity in the supine position.
2. Uninhibited contractions on supine filling.
3. Induced instability on standing, coughing or marking time.

Table 2 Nocturnal Enuresis

	Nights wet/week						
	¼-1	*2*	*3*	*4*	*5*	*6*	*7*
Male	7	5	4	3	3	1	9
Female	6	4	2	4	0	4	13
Total	13	9	6	7	3	5	22

Table 3 Symptoms as Percentage of Total

	All	*Male*	*Female*
Frequency	74	66	82
Urgency	69	69	70
Urge incontinence	43	34	52

Nine of 13 patients with nocturnal incontinence alone had cystometrically abnormal bladders compared with 2 out of the 11 patients of Whiteside and Arnold (1975); 4 were hypertonic and 5 showed uninhibited contractions. It is surprising that instability was associated with no diurnal symptoms in these 5 cases and suggests a sensory deficiency when the detrusor contracts on cystometric testing.

Symptoms Related to Instability

1. Frequency of micturition, less than 2-hourly, was present in 57% of cases; instability was present in 26 of these 32 cases (Table 4).

There is a significant correlation between frequency and instability using the chi-squared test, contrary to the findings of Torrens and Collins (1975).

2. Urgency was defined as the time the patient was able to postpone voiding; at least 15 min was regarded as normal (Table 5). Urgency occurred equally between the sexes (22 males, 23 females). Fifty per cent of the females had stable bladders, whereas nearly all of the males had unstable bladders. The female probably has 2 methods by which urgency is produced—an uninhibited detrusor contraction and a premature urethral relaxation.

3. Urge incontinence was divided into 3 groups

Table 4 Frequency of Micturition

	Hours							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Male	6	11	4	5	3	2	0	0
Female	11	9	7	4	2	1	0	0
Total	17	20	11	9	5	3	0	0

Table 5 Urgency of Micturition

	Severe	*Moderate*	*Mild*	*None*
Male	3	11	8	10
Female	9	8	6	10
Total	12	19	14	20

(Table 6). There was a significant relationship between incontinence and instability in the female but no such relationship was found in the male. This reflects the ability of the male to prevent incontinence by contracting his more powerful distal urethral sphincter complex.

4. Nocturnal enuresis and nocturia. There was no relationship between nocturnal enuresis and instability. There was, however, a significant relationship between nocturia and instability.

Discussion

The enuretics who at no time in their life experienced periods of dryness exceeding 3 months were defined as primary enuretics. The period of 3 months is arbitrary but it is used because a different pathological process is unlikely to account for similar symptoms occurring within such a short period of dryness. This group is divided into those who have no abnormality of diurnal micturition and those who have. The latter group are said to have the enuretic syndrome. The justification for this division on symptomatic assessment is strengthened by cystometric findings. A significant correlation was found between frequency and bladder instability. However, it was noted that 69% of primary nocturnal enuretics without day-time symptoms were also cystometrically abnormal. This result is at variance with the findings by Whiteside and Arnold (1975) of cystometric abnormality in only 2 out of 11 cases with nocturnal enuresis alone. The discrepancy is accounted for in 2 ways. Firstly, a rigid definition of day-time symptoms was adhered to in this series and the 5 cases of instability did have a tendency to increased frequency, particularly with high fluid intake; secondly, the occurrence of a non-contractile hypertonic bladder was defined as abnormal in this series.

Table 6 Urge Incontinence

	Every day	*2-3 × week*	*Occasionally*	*Never*
Male	1	2	8	21
Female	7	2	8	16
Total	8	4	16	37

The recurrent enuretics were included as it was felt that the primary cause of the recurrent enuresis had simply become latent. These patients often had persistent diurnal symptoms when the nocturnal enuresis had subsided, the male patients relapsing particularly after beer drinking. It seems that fluid loading, the effect of beer upon the detrusor and the increased depth of sleep caused by alcohol combine to cause incontinence.

The nocturnal enuretic with diurnal incontinence frequently has an uninhibited bladder. Seven of the 8 patients with severe urge incontinence were female, reflecting the weakness of the voluntary muscle of the female external sphincter. Forty-three per cent of all cases admitted regular incontinence. It has been suggested that children with both diurnal and nocturnal enuresis take longer to gain bladder control than those with nocturnal enuresis alone (Hallgren, 1957).

Hallgren (1957), Notschaele (1964) and Forsyth and Redmond (1974) reported that 25% of enuretic children had both diurnal and nocturnal incontinence. It thus appears that diurnal incontinence is twice as common in adult enuretics as in younger enuretics.

The incidence of enuresis diminishes with age. Theoretically, spontaneous remission should occur until all cases caused by delayed development are dry, unless development is prevented by unknown factors.

Remission rates have been calculated at 14 to 17% per annum (Forsyth and Redmond, 1974) between the ages of 5 and 20 years. Three per cent of their series were still enuretic at 20 and they report known remission up to the age of 30. The present series has cases persisting into their 40s and even 50s, usually with severe diurnal symptoms. Few cases of nocturnal enuresis alone persisted beyond the age of 25.

There was no sex bias in this series, unlike the commonly found male predominance in childhood. Many were severe: 50% wet the bed more than 26 nights per month and 34% had wet the bed nearly every night of their lives. Paediatric surveys record a similar incidence in children and suggest that the frequency of bed wetting bears no relationship to the rate of spontaneous remission.

Deep sleep is frequently suggested as being a critical factor in the genesis of enuresis and an excessive proportion of slow wave sleep is found in EEG studies. Seventy-five per cent of our cases described themselves as deep sleepers.

The diurnal symptom of frequency was present in 57% of the adults. De Jonge (1973) reported an incidence of only 15% in children. The higher incidence in adults, particularly in females, may be associated with a high incidence in the normal population at this age, although frequency in adults is significantly related to instability of the bladder.

The urodynamic findings in the primary enuretics were difficult to explain in some cases. The occurrence of a stable bladder in a male patient with severe diurnal symptoms may reflect the failure of our cystometric method to stress the bladder as effectively as the method used by Whiteside and Arnold (1975). In females the finding of stability with severe diurnal symptoms means either a pure sensory dysfunction or an overinhibited sphincter mediated through S4 (Torrens, 1974). The patients with stable hypertonic bladders had large insensitive bladders, suggesting a deficiency in the sensory pathways. A defect in the reception or transmission of impulses from the detrusor tension receptors may cause a failure of reflex receptive relaxation of the smooth muscles and, secondly, a failure of impulses to reach conscious levels. No motor failure was seen in these patients as they voided at normal detrusor pressures and flow rates. In the patient who is insensitive to uninhibited contractions, 2 sensory abnormalities may be indicated: firstly, a failure of the vegetative inhibitory reflexes to prevent a detrusor contraction and, secondly, a failure of the cortical afferent projections despite maximal stimulation of the bladder motor centre.

The occurrence of nocturnal enuresis and the frequent coexistent symptoms of frequency, urgency and urge incontinence seem to parallel closely the findings in children. The cystometric findings show a positive correlation between frequency, nocturia and urge incontinence and uninhibited detrusor contractions. There are, however, several cystometric findings in adult enuretics which suggest that the pathophysiological process is varied and each case must be assessed before rational therapy can be instituted.

It is concluded that a bladder abnormality, together with deep sleep, is a major cause of persistent primary enuresis.

Acknowledgements

We wish to thank Mr W. Keith Yeates for his constant advice. We also thank Mr Yeates, Mr D. M. Essenhigh and Mr R. R. Hall for referring their patients for investigation. Miss Christine Murley provided invaluable help with the pressure/flow studies. J R.H. was a Northern Counties Kidney Research Fellow when this work was done.

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The Relevance of Urinary Sampling Methods in Patients with Indwelling Foley Catheters

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Summary—The relevance of different urinary sampling methods in male patients with indwelling catheters was studied. There was good agreement between the bacterial strains cultured from urine sampled at the *catheter end* compared to samples obtained by *catheter puncture.* However, one-quarter of the samples obtained by the catheter did not show complete agreement with the *bladder aspiration samples.* It is concluded that, in patients with an indwelling catheter, urinary sampling by the catheter does not always provide relevant information about the bacterial strains present and bladder aspiration is advised.

Indwelling bladder catheters inevitably give rise to bacterial colonisation of the urinary tract, although a closed drainage system or antibiotic treatment can delay the time of onset.

This study evaluated the different urinary sampling methods used in patients with Foley catheters. The sample can be obtained either by aseptic needle puncture of the catheter or by collecting urine directly from the catheter end. Needle puncture is claimed to be preferable in order to avoid bacterial contamination of the sample. The results from the 2 sampling methods were compared with the results achieved by bacterial culturing from samples obtained by suprapubic bladder aspiration.

Patients and Methods

Forty-three male patients (mean age 73 years, range 52-89) with indwelling catheters were studied. None had undergone any recent instrumentation other than the catheter insertion. The patients on this form of drainage were either waiting for prostatic surgery or were unfit or had refused operation. All catheters were clamped and were opened only intermittently. Samples were obtained from 2 patients on 3 occasions, and from 3 patients on 2 occasions; sampling was thus performed on 50 occasions. Twenty-five (50%) samples were obtained from hospitalised patients; 22 (44%) samples were from patients receiving antibiotic treatment. Thirteen (26%) samples were obtained from patients who had had the indwelling catheter for 10 days or less, 13 (26%) from those who had had the catheter for 11 to 30 days and the other 24 (48%) from patients with indwelling catheters for more than one month.

After clamping the catheter for at least 2 hours, 3 samples were taken from each patient:

1. After cleansing the skin with an alcoholic disinfectant (pad saturated with 70% isopropyl alcohol) suprapubic bladder puncture was performed and urine was aspirated into a sterile syringe.
2. After cleansing (pad saturated with 70% isopropyl alcohol), the proximal extraurethral part of the catheter was punctured with a needle and a urinary sample was obtained with a sterile syringe.
3. A urine sample was obtained by letting the urine flow from the catheter end into a sterile test tube.

It was difficult to puncture the bladder unless the catheter had been closed for more than 2 h. No complications occurred except for the Foley balloon being punctured occasionally and a new catheter having to be inserted. The samples were brought to the bacteriological laboratory within 1 h and either cultured at once or kept at +4°C and cultured within 4 h. The calibrated loop-streak plate culture method was used to detect bacteria in urine. Plating media were blood-agar and a bromothymol blue lactose medium. All plates were incubated at +37°C under aerobic conditions. Bacteriuria was considered significant in catheter urine with a viable count exceeding

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Table 1 Frequency of Bacterial Strains Found by Suprapubic Bladder Aspiration. (Only the First Culture From Each Patient)

Number of patients with growth of		
Streptococcus faecalis	10/43	23%
Klebsiella pneumoniae	9/43	21%
Escherichia coli	7/43	16%
Staphylococcus aureus	2/43	5%
Staphylococcus epidermidis	3/43	7%
Proteus mirabilis	4/43	9%
Proteus rettgeri	2/43	5%
Pseudomonas aeruginosa	2/43	5%
Other aerobic bacterial strains (*Acinetobacter anitratus, Bacillus coagulans, Streptococcus pyogenes*)	3/43	7%
Yeast strains	3/43	7%

100,000 bacteria per ml. Bacterial growth from bladder aspiration samples was always considered significant. Where growth did occur in the bladder urine, the viable counts were always in excess of 1000 per ml. Gram-negative rods were identified by conventional biochemical tests (Cowan and Steel, 1970).

Streptococci were identified by tests for haemolysin production, aesculin hydrolysis and the CAMP-test.

The identification of staphylococci was performed by tests for DNAase activity and novobiocin sensitivity.

The paper disc method (Ericsson and Sherris, 1971) was used for susceptibility testing (commercial antibiotic sensitivity discs AB Biodisk Solna Sweden). The bacterial strains of the same species isolated from different samples were then identified by means of the sensitivity pattern.

Results

Nineteen (38%) of the suprapubic puncture samples yielded no growth of aerobic bacteria; of the remaining samples 15 yielded more than one strain on culture (Table 1).

Of the 22 samples obtained from patients receiving antibiotic treatment 14 (64%) were sterile compared with 5 (18%) of the 28 samples from patients without antibiotic treatment.

Of the 24 samples obtained from patients with the catheter indwelling for more than one month 2 (8%) were sterile compared with 17 (65%) of the 26 samples from patients with the catheter *in situ* for less than one month.

A comparison of the results of sampling from the *catheter-end and catheter-puncture* showed total agreement between the bacterial strains cultured in 45 (90%) of the 50 sample pairs. A strain cultured in only one of the samples (partial agreement) was found in 5 (10%) of the sample pairs (Table 2).

Bladder aspiration compared with catheter puncture showed complete agreement between the cultures obtained in 38 (76%) of the 50 sample pairs. Of these, 13 yielded no growth in both samples. Seven (14%) showed partial agreement: all except one of the patients had had the catheter for more than one month and all except one were without antibiotics (Table 3). All patients had a massive growth of *Klebsiella pneumoniae*, or in one case, *Proteus mirabilis* in both samples, and all except one patient had an additional bacterial strain in the sample obtained by catheter puncture.

No agreement between the cultures from the 2 sampling techniques was found in 5 (10%) of the sample pairs. These 5 patients had had the catheter for less than one month. Two of them had different strains in the 2 samples. In 3 patients the bladder aspiration sample yielded no growth,

Table 2 Comparison Between Samples Obtained by Catheter Puncture and Samples Collected From the Catheter End (50 Samples)

	Catheter time	*Antibiotics*	*Cultures obtained by both sampling methods*	*Cultures obtained only via catheter end sampling*	*Cultures obtained only via catheter puncture*
Partial Agreement					
Patient No. 1	years	No	*Proteus mirabilis*	—	*Streptococcus faecalis*
Patient No. 2	3 months	No	*Proteus inconstans* *Streptococcus faecalis*	—	*Staphylococcus epidermidis*
Patient No. 3	5 months	No	*Klebsiella pneumoniae* *Streptococcus faecalis*	—	*Pseudomonas aeruginosa*
Patient No. 4	5 weeks	No	*Escherichia coli*	Microcuccus species	—
Patient No. 5	7 months	No	*Klebsiella pneumoniae* *Proteus rettgeri*	—	*Steptococcus faecalis* (also by bladder aspiration)

Table 3 Comparison Between Samples Obtained by Catheter Puncture and by Suprapubic Bladder Aspiration (50 Samples)

	Catheter time	*Antibacterial drugs*	*Cultures obtained by both sampling methods*	*Cultures obtained only by suprapubic aspiration*	*Cultures obtained only by catheter puncture*
Partial agreement:					
Patient No. 9	4 months	No	*Klebsiella pneumoniae* *Streptococcus faecalis*	—	*Proteus morganii*
Patient No. 1	years	No	*Proteus mirabilis*	—	*Streptococcus faecalis*
Patient No 10	5 months	No	*Klebsiella pneumoniae* *Streptococcus faecalis*	—	*Pseudomonas aeruginosa*
Patient No. 11	3 months	Ampicillin	*Klebsiella pneumoniae*	—	*Acinetobacter anitratus*
Patient No. 12	years	No	*Klebsiella pneumoniae*	—	*Proteus mirabilis*
Patient No. 13	1 month	No	*Klebsiella pneumoniae*	—	*Proteus mirabilis*
Patient No. 14	3 days	No	*Klebsiella pneumoniae*	*Escherichia coli*	—
No agreement					
Patient No. 15	10 days	No	—	—	*Streptococcus faecalis*
Patient No. 16	2 days	No	—	*Staphylococcus epidermidis*	*Escherichia coli*
Patient No 2	3 months	No	—	*Streptococcus pyogenes* (*Torulopsis glabrata*)	*Streptococcus faecalis* *Proteus inconstans* *Staphylococcus epidermidis*
Patient No. 4	1 week	Nitrofurantoin	—	—	*Escherichia coli*
Patient No. 4	3 weeks	No	—	—	*Alicaligenes faecalis*

whereas growth occurred in the sample obtained by catheter puncture.

Discussion

Urine sampling and bacterial culture are performed in patients with indwelling Foley catheters in order to detect and follow the bacterial invasion that is known to occur. The closed drainage system delays the bacterial invasion, but it is still essential to know the composition of the bacterial flora in order to administer the appropriate antibiotics if complications occur. Sampling by catheter puncture rather than urinary sampling from the catheter end has been recommended so that the closed system is maintained (Dale, 1975). It is also claimed that catheter puncture reduces the risk of bacterial contamination during the sampling (Fincke and Friedland, 1976).

A comparison of the results of the 2 sampling methods indicated complete agreement between the bacterial strains cultured in 45 (90%) of the 50 sample pairs. Five (10%) revealed only partial agreement between the results of the 2 methods. The difference can in most cases be explained by difficulties in the isolation as overgrowth of coliform rods makes it difficult to isolate Gram-positive cocci. It is notable that this difference always occurred in patients with the catheter *in situ* for more than one month and without antibiotic treatment. Obviously, both methods give equally representative results concerning the bacterial flora of the catheter urine.

The normal bladder has several defence mechanisms against bacterial invasion (Cox and Hinman, 1965; Kaye, 1975). The effectiveness of these mechanisms is jeopardised by the use of an indwelling catheter, as the catheter system and urinary tract sooner or later are colonised by bacteria, which in many cases leads to a true infection. On 3 occasions, in patients catheterised for less than one month, the bladder aspiration sample was sterile when there was a significant growth in the urine obtained by the catheter. Thus it seems that the defence mechanisms of the bladder can delay the bacteria from reaching the bladder while they multiply in the stagnant catheter urine.

Even when the bacterial invasion has reached the bladder urine, the catheter urine can contain strains not found in the bladder; this occurred in 9 sample pairs. With one exception, this happened in patients without antibiotic treatment and catheterised for at least one month. This suggests that even in these patients the bladder can at least protect itself from some of the bacterial strains. It is notable and hitherto unexplained that, in the patients with partial agreement between bladder and catheter urine, *Klebsiella pneumoniae* was found in the bladder in all except one patient.

In all 14 (28%) of the sample pairs where the catheter urine was sterile, the bladder aspiration sample was also sterile. But of the 36 (72%) catheter urine samples with significant bacteriuria, no total agreement with the bladder aspiration sample was found in fully 12 of the sample pairs. It must be concluded that catheter urine sampling often fails to provide relevant information about the bladder urine in male patients with indwelling catheters; to obtain this information bladder puncture is the only reliable method.

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Vesical Leukoplakia

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Summary—Thirty-two patients with vesical leukoplakia have been seen in the St Peter's group of hospitals during the past 20 years. Twenty-five (78%) were men and 7 (22%) women with an average age at diagnosis of 55 years. Seventeen (53%) had a history of chronic or recurrent urinary infection whilst 9 (28%) had previously developed bladder stones.

Nine patients (28%) have so far developed a carcinoma of the bladder in association with the leukoplakia and, of these, 4 are dead, 2 having died of metastatic disease and 2 in the immediate post-operative period. Eight of the 9 malignancies were squamous carcinomas.

Leukoplakia of the bladder is a rare condition with a sinister reputation. Translated literally, leukoplakia means "white plate" and is a descriptive term originally introduced by Schwimmer (1877) to describe any white mucosal plaque at a variety of sites. Whilst vesical leukoplakia is now widely used as a diagnostic term, we believe that it is essentially a clinical diagnosis and suggest that its use should depend upon the clinical finding of a white plaque which proves on histological examination to be stratified squamous epithelium showing keratinisation. The latter criterion thus excludes the "vaginal" type of squamous metaplasia seen so frequently at the bladder neck in women (Packham, 1971).

As reports of series of cases of vesical leukoplakia are uncommon we have reviewed a group of patients with this disorder who have been seen in our hospitals during the past 20 years.

Patients and Methods

In all, 35 cases of vesical leukoplakia were recorded in the files of the Department of Pathology of the St Peter's Hospitals, the diagnoses having been made between the years 1959 and 1978 by one of 2 consultant pathologists. Where necessary, details of the course of the patient's illness were obtained from the hospital records, supplemented by letters written to the patients and their medical practitioners.

Thirty-two patients were available for study, 3 having been excluded because of inadequate follow-up. Twenty-five were men and 7 (22%) women. Ages at presentation varied from 14 to 81 years with an average of 55 years (Fig. 1). There was a wide range of occupations and social class. At the time of presentation 23 patients (72%) gave a history suggestive of urinary infection with pain and frequency on micturition. Sixteen (50%) had experienced difficulty in voiding and 9 (28%) had seen blood in their urine at some stage. Five (16%) had commented upon the passage of white flakes and debris.

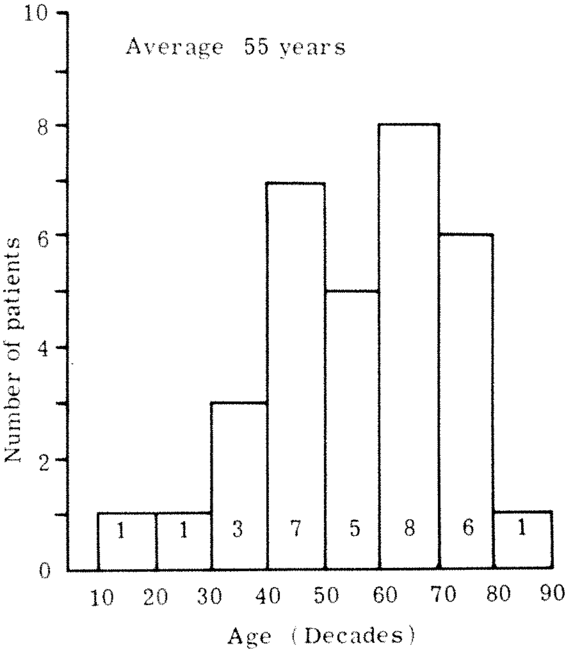

Fig. 1 Vesical leukoplakia: ages at diagnosis.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Over half of the group had a past history of chronic or recurrent urinary infection (Table 1). Thirteen (41%) had formed urinary stones and 9 (28%) had required the operative removal of stones from the bladder. Seven of the men had been treated for urethral strictures. Three had had their strictures dilated for more than 20 years and all but one had a sorry history of abscesses and urethral fistulae. Five developed leukoplakia between 5 and 24 years after the diagnosis of a transitional cell carcinoma of the bladder, the leukoplakia having been found at check cystoscopy. Four of these 5 had initially had pTa tumours (UICC, 1978) treated variously by resection, fulguration, the instillation of Epodyl or the implantation of radon seeds. One woman with a pT1b tumour had received a course of radiotherapy. Three of the 5 had been clear of a superficial tumour for an average of 11 years and in these 3 the leukoplakia was seen to occupy a site on the bladder wall away from the original tumour.

Four had undergone some form of prostatectomy. One had a neurogenic bladder and another a closed exstrophy.

Urine cultures were positive in 23 (72%), with *Proteus* (11) and *Esch. coli* (7) the predominant organisms. In each case an intravenous urogram had been performed shortly before the leukoplakia was diagnosed. Of the 31 available for review only 6 were normal. The abnormalities encountered are summarised in Table 2. All patients were cystoscoped: frequently comment was made upon the poor initial view due to the "snowstorm" effect of white cellular debris.

The areas of leukoplakia were variously described as shaggy, membranous or encrusted. Sometimes a distinct edge could be identified. The distribution was recorded in 31 cases, in 6 of which the whole bladder was involved, though the ureteric orifices were spared in 2. Eighteen had localised areas but in 7 of these more than 30% of the bladder was involved. In the remaining 7 the presence of leukoplakia was unsuspected as the area was hidden within a diverticulum. On one occasion a tumour was seen within a bladder totally involved by leukoplakia. It is worth recording that 8 patients had been known to have normal cystoscopic appearances prior to the diagnosis of leukoplakia.

Table 1 Vesical Leukoplakia: History

	Number	*(%)*
Chronic or recurrent urinary infection	17	(53%)
Urinary stone renal 4 vesical 9	13	(41%)
Urethral stricture	7	(22%)
+ fistulae 6		
+ ischiorectal abscesses 2		
Bladder neoplasm (TCC)	5	(16%)
Prostatectomy	4	(12%)
Neurogenic bladder	1	(3%)
Closed exstrophy	1	(3%)

Table 2 Vesical Leukoplakia: Radiology (31 Cases)

Intravenous urogram	*Normal:*	*6 (19%)*
	Abnormal:	*25 (81%)*
Residual urine		9
Diverticula		9
Hydronephrosis		8
Stone: kidney		3
Bladder		4
Pyelonephritis		3

Histological confirmation was obtained in all cases by examination of either biopsy material or excised diverticula. In each of the latter, patches of thick white epithelium were noted on macroscopic examination. Microscopically, the urothelial changes were essentially of the 2 types designated atrophic and hypertrophic by O'Flynn and Mullaney (1967). In the first the stratified squamous epithelium was thin with a flat undersurface, a stratum granulosum and a variable amount of keratinisation (Fig. 2). The second type was characterised by hyperplasia of the prickle layer with the formation of rete pegs (Fig. 3). Parakeratosis was common in this variety and the granular layer was therefore usually absent. The distinction is somewhat artificial, however, as both appearances could be seen on occasion within a single biopsy or in the same case at different times. Non-keratinised stratified squamous epithelium, sometimes of vaginal type, could also coexist with the keratotic varieties. When first diagnosed, a predominantly atrophic appearance was seen in 22 (69%) of the patients in this series, while in the remaining 10 (31%) the picture was predominantly hypertrophic.

In 3 cases, at presentation, there was associated malignant change. Two patients had invasive tumours—one squamous and one anaplastic. Only one of these had been recognised at cystoscopy, the other being discovered by random biopsy of leukoplakic areas. In the third case a focus of non-invasive squamous carcinoma was present in an area of leukoplakia within a resected diverticulum.

Treatment and Results

Where present, urinary infections were treated by the appropriate antibiotics.

In the 7 cases with diverticular disease the affected tissue was removed by diverticulectomy. Five are alive more than 9 years later (including the patient with *in situ* squamous malignant change), and all remain symptom free. Two are dead: one was well for 9 years before being killed in an accident and the other died of other causes a year after diverticulectomy.

Of the 25 cases in which leukoplakia was confined to the bladder wall, 17 are alive and 8 have died (Table 3). Ten of those still alive are symptom-free 1 to 15 years after the diagnosis of leukoplakia. All are cystoscoped regularly. In 6 the areas of leukoplakia have remained stable in distribution, whilst in 2 others they have been increasing in extent for periods of between 1 and 9 years after diagnosis. In 2 cases the bladders are clear of disease 2 and 3 years after the destruction of small areas by resection and fulguration.

Three other patients among the 17 survivors have undergone a palliative urinary diversion 1 to 3 years after diagnosis, 2 because of severe frequency and bladder pain and one because of the risk of malignant change.

The remaining 4 who are still alive have developed squamous malignant change in areas of leukoplakia (Table 4). Two developed invasive tumours 1 to 17 years after the leukoplakia was first diagnosed. One is well 2 years after a cystectomy and diversion, whilst the other man has survived 3 years after a partial cystectomy, only to develop a recurrence of tumour in a remaining area of leukoplakia. The other 2 have recently developed *in situ* non-invasive squamous malignant change in areas of leukoplakia which were

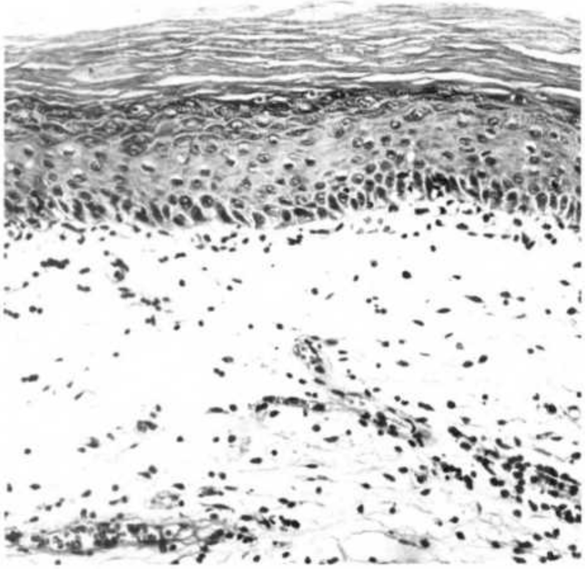

Fig. 2 Vesical leukoplakia of atrophic type consisting of keratinised stratified squamous epithelium with flat undersurface (H and E ×40).

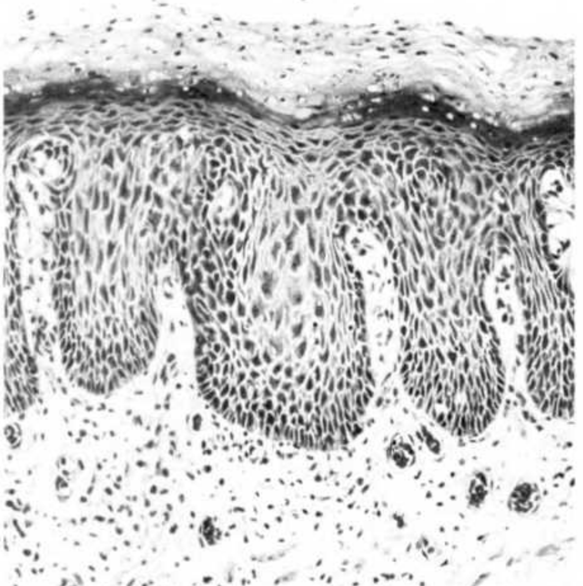

Fig. 3 Vesical leukoplakia of hypertrophic type with parakeratosis and rete pegs (H and E ×40).

Table 3 Vesical Leukoplakia

Site	*No.*	*Alive*	*Dead*	*Malignant change*
Diverticulum	7	5	2	1
Bladder wall	25	17	8	8
Total	32 (100%)	22 (69%)	10 (31%)	9 (28%)

Table 4 Vesical Leukoplakia: Malignancy

Site	*Dead*	*Alive*	*Total*
Diverticulum			
Leukoplakia + malignancy	0	1	1
Bladder wall			
Leukoplakia + malignancy	2	0	2
Leukoplakia – malignancy	2	4	6
Total			9 (28%)

present for 2 and 19 years respectively. In both cases the diagnosis of malignant change was obtained after repeated random endoscopic biopsies. Neither has yet had further treatment.

Of the 8 patients who are dead, 4 died of causes unrelated to their bladder lesion 1 to 7 years after diagnosis and in all the area of leukoplakia had remained unchanged, with no evidence of malignant transformation. Each of the 2 cases in which a malignant neoplasm was found at the same time as the leukoplakia died shortly after diagnosis (Table 4), one of peritonitis after a urinary diversion and the other of a myocardial infarct after the initial bladder biopsy. Two patients developed an invasive squamous carcinoma in an area of leukoplakia one and 10 years after the leukoplakia was first seen. Both died of metastatic disease within a year of a radical cystectomy and diversion.

Altogether 9 patients (8 men and 1 woman) had areas of leukoplakia associated with malignant change and of the 9, 4 initially had the hypertrophic type of leukoplakia, while 5 had the atrophic type.

In those cases which progressed to neoplasia there is no record of any alteration in urinary symptoms or cystoscopic appearances that gave an adequate warning of malignant change, although in 2 the area of leukoplakic involvement was seen to increase.

Discussion

The changes of vesical leukoplakia were first reported in 1861 by Rokitansky, who termed it a cholesteotoma. The various theories of aetiology have been comprehensively reviewed elsewhere (Holley and Mellinger, 1961) but the association with chronic urinary infection and stone suggest that it may be a reponse to continued inflammation and irritation of the bladder. That it is probably an acquired lesion is further supported by our finding that 8 patients in this series had previously had bladders which were cystoscopically free of leukoplakia.

The apparent progression to malignancy has been stressed by O'Flynn and Mullaney (1967, 1974) who found a 25% association with malignant change. In this series, if the 3 cases in which malignancy was diagnosed at the same time as the leukoplakia are included with those 6 that subsequently developed malignant change, we have found an overall association between leukoplakia and malignancy of 28%, which is in keeping with the findings of O'Flynn and Mullaney. Like them, we also found no significant difference in the incidence of malignant change or subsequent behaviour of the atrophic as distinct from the hypertrophic type of leukoplakia.

The problem of what constitutes the best management of patients with vesical leukoplakia remains unresolved. If *in situ* malignant change precedes invasion, then clearly its early detection by biopsy is of value. Unfortunately, invasive change can equally well occur and both may go undetected beneath the mantle of leukoplakia. Modern endoscopic biopsy forceps usually provide an adequate depth of tissue for examination, but random sampling may clearly miss an early tumour. Prophylactic cystectomy remains an option, but the symptomless patient will find this an unattractive solution.

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Computed Tomography as an Adjunct to Bimanual Examination for Staging Bladder Tumours

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Summary—Computed tomography (CT scanning) has been undertaken in 51 patients with bladder tumours, 15 of whom subsequently had pathological examination of the bladder to confirm the extent of tumour spread. Concordance between the CT and pathological staging (80%) was as good as that between clinical and pathological staging (73%). Most of the inaccuracies of clinical staging were underestimations of the extent of muscle invasion, whilst the inaccuracy of CT involved overstaging.

The principal areas where CT might improve the accuracy of clinical staging are in patients with invasive tumours who after transurethral resection have no mass palpable on bimanual examination, and in patients following radiotherapy who might be candidates for salvage cystectomy but in whom assessment of the spread of tumour is difficult because of post-irradiation fibrosis. Data from a much larger series are required to ascertain whether the additional information provided by CT will produce any improvement in patient management.

In the management of bladder cancer Jewett (1952) was the first to demonstrate the important prognostic significance of the extent of muscle invasion. The current standard procedures for assessing this are cystoscopy, biopsy and bimanual examination under anaesthesia. The bimanual examination is the least accurate of these staging procedures, especially in obese patients. Several authors have established that there is a 15 to 20% degree of inaccuracy between clinical and pathological staging when cystectomy specimens from otherwise untreated patients are examined histologically (Whitmore *et al.*, 1977), or when the bladder is assessed at open operation (van der Werf-Messing, 1978). The main inaccuracy is underestimating the extent of muscle invasion. After treatment with radiotherapy the discordance between clinical staging and pathological staging of the cystectomy specimen is higher, sometimes as high as 50% due to both understaging and overstaging (Whitmore *et al.*, 1977; van der Werf-Messing, 1979). In an attempt to improve the accuracy of staging we have used computed tomography (CT scanning) as an adjunct to cystoscopy, biopsy and bimanual examination.

Material and Methods

In this preliminary report we have compared CT scanning with conventional staging in 51 patients. Pathological correlation was available in 15 of these cases; in 12 of them the pathology was from cystectomy specimens, in one from a post mortem examination, and in 2 patients with T4 tumours it was from operative examination and biopsy during urinary diversion procedures for severe bladder symptoms. All of the patients were referred to one of us (R.T.O.) for entry into chemotherapy studies. Routine staging according to the UICC (1978) classification was performed following transurethral resection of intravesical tumour. CT examination was performed between 1 and 2 weeks after the cystoscopy. The patients undergoing cystectomy had all had radiotherapy. CT scans and clinical staging were performed immediately before operation in these patients.

Technique for Scanning

All patients were encouraged to have a full bladder for the examination. Occasionally a diuresis was induced with 20 mg intravenous frusemide. The difference in density between the urine and the bladder wall was sufficient to define the latter and we did not find it necessary to use intravenous contrast medium. Prior to the

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979

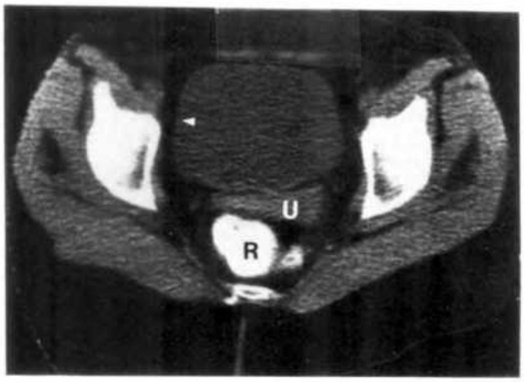

Fig. 1 Normal female pelvis with thin bladder wall (arrow) outlined by pelvic fat and urine. Uterus (U); gastrografin in rectum (R).

scan, oral Gastrografin 5% (sodium meglumine diatrizoate) was given to outline the small bowel and Gastrografin and air were injected rectally to outline the colon and rectum. To avoid artefacts caused by peristalsis during the scan, 20 mg Buscopan (hyosine-N-butylbromide) were given intravenously. Whenever possible, in female patients, a tampon was inserted to identify the vagina. Serial images were taken from the symphysis pubis to the level of L5 at 1.5 cm intervals (slice thickness 13 mm, scan time 20 s). The images were reviewed and classified by 3 radiologists (M.J.K., J.H., I.K.F.) in ignorance of the clinical stage of the tumours. Normal appearances on CT scanning in a male and female pelvis at the level of the hip joints are illustrated in Figures 1 and 2.

Criteria for CT Staging

As CT staging was performed after transurethral resection of intravesical tumour plus associated superficial muscle, it was assumed that Stage 1 and Stage 2 tumours would not be detectable. On this basis all patients in whom there was no localised thickening of the bladder wall on CT were staged as less than Stage 3 (Fig. 3). (Note the generalised thickening due to the effect of previous radiotherapy.) Those patients in whom a clearly defined localised thickening of the bladder wall was demonstrable were classified as Stage 3 (Fig. 4), and those where there was continuity between the tumour mass and a normal local structure (Fig. 5) or in whom the mass extended to the lateral pelvic wall (Fig. 6) were defined as Stage 4. Although it appears possible to divide Stages 3 and 4 into subcategories A and B on the CT images, such distinction would not have altered treatment at the present time, and in the analysis of this small series we have

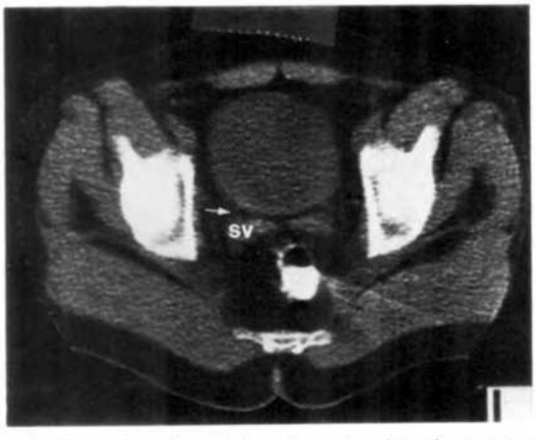

Fig. 2 Normal male pelvis. Note the fat plane (arrow) between the seminal vesicles (SV) and the bladder.

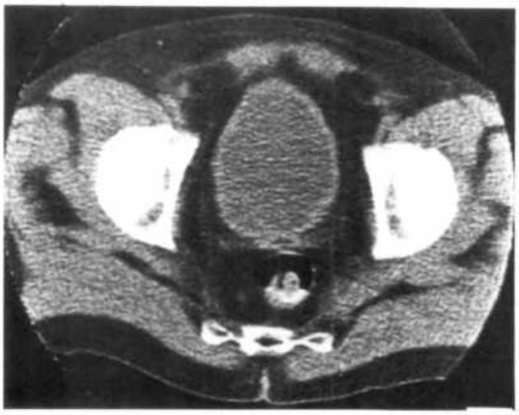

Fig. 3 Generalised thickening of bladder wall after radiotherapy for recurrent T1 tumour. No tumour mass on CT or in cystectomy specimen. CT staging as less than Stage 3.

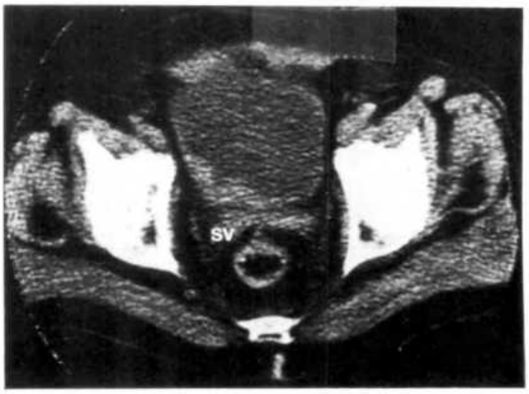

Fig. 4 Right-sided tumour involving full thickness of bladder, clearly separate from the seminal vesicle (SV). Cystectomy specimen confirmed CT staging of Stage 3.

Table 1

Cystectomy specimen pathological P stage	*No. of patients*	*CT staging*		
		<3	*3*	*4*
<3	6	④	1	1
3	4		④	
4	5		1	④

divided the tumours simply into 3 groups, those less than Stage 3, Stage 3 and Stage 4.

Results

Table 1 compares the CT staging with the pathological staging in the 15 patients with pathological correlation. Concordance was seen in 12 patients. One patient was understaged by the CT scan and 2 were overstaged. The following case reports show these discrepancies between CT and pathological staging.

Case Reports

Case 1. A 50-year-old woman had a tumour at the base of the bladder causing bilateral ureteric obstruction. She had already received radiotherapy before being referred to St Peter's Hospitals. The clinical assessment of a T2 tumour was confirmed by the pathological staging after cystectomy. The pre-operative CT scan (Fig. 7) showed apparent thickening of the bladder wall posteriorly, therefore interpreted as a Stage 3 tumour. This could, of course, have been residual superficial tumour or oedema following the endoscopic resection.

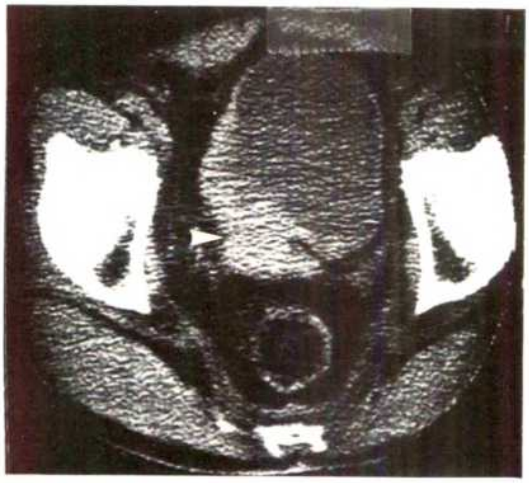

Fig. 5 Tumour invading the right seminal vesicle with loss of the interposed fat (arrow). Pathological confirmation of a Stage 4A tumour.

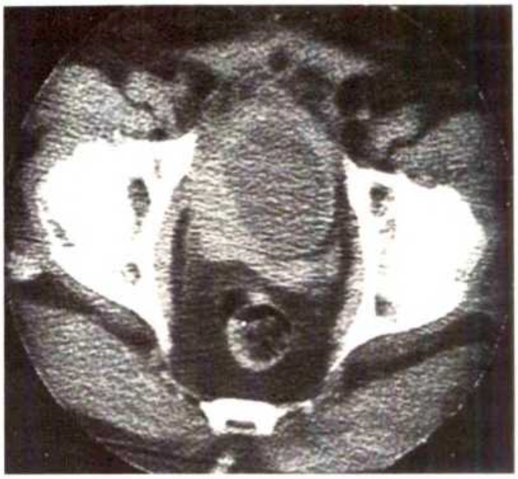

Fig. 6 Fixed mass clinically. Tumour extending into the right seminal vesicle and out to the wall of the pelvis. CT staged as 4B.

Case 2. The second case which was overstaged by CT was a patient examined 18 months after radiotherapy. Clinical staging was difficult because post-irradiation fibrosis suggested that the bladder was fixed to the pelvic wall and the biopsy showed invasive tumour. The CT scan (Fig. 8) showed thickening of the bladder wall on the right with obliteration of the seminal vesical angle interpreted therefore as a Stage 4A tumour. The patient received chemotherapy, but follow-up CT and clinical staging showed no change. Because of his severe symptoms from an irritable bladder and in the absence of detectable metastases, he was explored and it was found possible to remove his bladder. Subsequent pathological sections demonstrated a small tumour invading the superficial muscle only. Both the clinical assessment and the CT scan had overstaged this tumour, although the CT had done so to a lesser extent.

Case 3. A patient who was understaged both clinically and on CT scan was a man with a widespread tumour involving nearly two-thirds of the intravesical surface

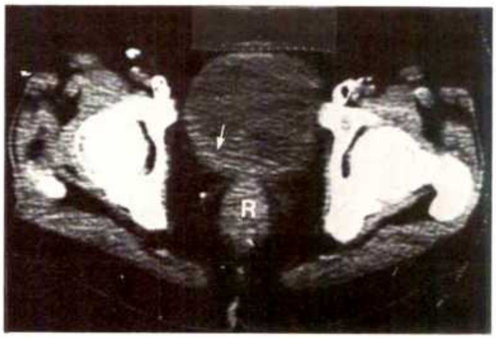

Fig. 7 Apparent thickening of the bladder wall posteriorly (arrow). Rectum (R). CT Stage 3 but pathological Stage 2.

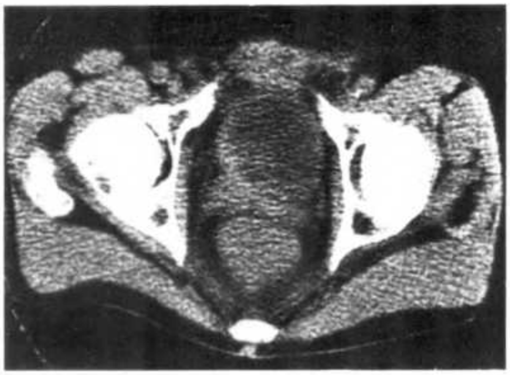

Fig. 8 Apparent tumour invading the right seminal vesicle (Stage 4A). Clinically T4B because of post-irradiation fibrosis. Cystectomy specimen Stage 2.

of the bladder. After resection of the tumour, examination under anaesthesia showed no mass either before or after radiotherapy. The CT scan just before cystectomy showed generalised thickening of the bladder wall, but in addition there were 2 areas of localised thickening associated with irregularity of the outer surface of the bladder on the left lateral and anterior walls (Fig. 9). These were thought to be 2 Stage 3B tumours. On the left of the bladder there was a mass of lower density thought to be an obstructed ureter. After cystectomy, examination of the specimen demonstrated that the mass outside the bladder was a diverticulum and not an obstructed ureter, and confirmed that there were 2 Stage 3B tumours which had not been detected clinically. Further sections through the prostate, however, showed it to be invaded by a third tumour, making this a pathological Stage 4.

Table 2 compares the CT versus pathological staging with the clinical versus pathological staging in the same group of patients. It can be seen that the overall accuracy is similar. The numbers are small, but the results would suggest that understaging is a greater problem with clinical examination than with CT, as illustrated by the following patient.

Table 2 Comparison of clinical and CT staging of Bladder Tumour

	N	*Concordance*	*Understaged*
CT *v.* pathological stage +	15	12	1
Pre-op. clinical *v.* pathological stage +	15	11	3

Case 4. This patient was referred for chemotherapy because of tumour recurrence in the bladder after initial reponse to radiotherapy. The tumour was resected transurethrally and at bimanual examination no mass was felt. Pathological staging of the biopsy was P2. After 2 courses of chemotherapy cystoscopy showed further recurrence, but after resection again no mass was palpable bimanually. CT scanning at this time showed a mass involving the full thickness of the bladder wall (Fig. 10). A cystectomy was performed and the pathological examination confirmed tumour invading the deep muscle.

Out of a total of 51 patients, one of the patients, who did not come to cystectomy, had a technically poor scan which was of no diagnostic value. There were, therefore, 50 patients available for comparison of the CT findings with the clinical staging. To assess the effect of radiotherapy on clinical and CT stage correlation we have divided the patients into 2 groups, 23 who

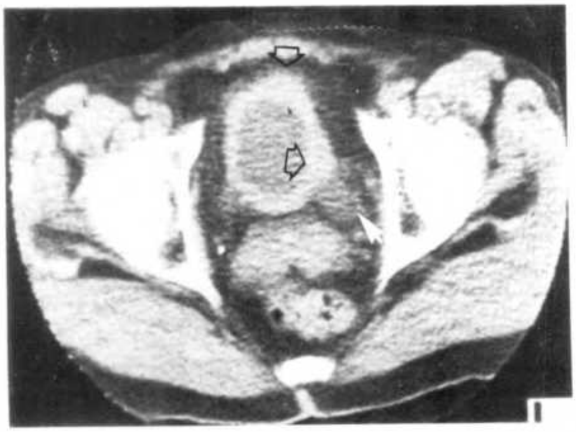

Fig. 9 Post-irradiation thickening. Two tumours (open arrows) extending through the wall (Stage 3B). Diverticulum (white arrow). Pathology showed prostate invaded (Stage 4A).

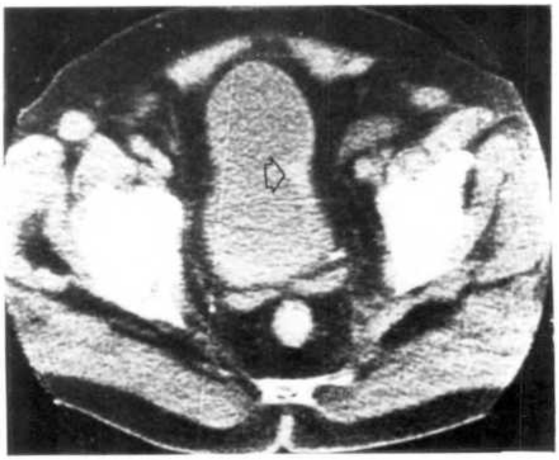

Fig. 10 Stage 3 tumour (arrow) undetected clinically. Pathology confirmed invasion of deep muscle.

Table 3

Clinical T stage	*No. of patients*	*CT staging in 23 untreated patients*		
		<3	*3*	*4*
<3	8	③	4	1
3	5		④	1
4	10			⑩

were assessed prior to radiotherapy and 27 staged after radiotherapy (Tables 3 and 4).

Table 3 shows that in the patients who had not received previous radiotherapy CT increased the stage in 6 cases, and no patient was staged lower on CT than on clinical examination.

Table 4 shows that 7 of the patients were staged higher on CT than on clinical examination and 3 were staged lower. These 3 were patients in whom clinical examination suggested a frozen pelvis with a mass fixed to the pelvic wall on bimanual examination.

Discussion

CT appears to be at least as accurate as clinical staging in detecting Stage 3 and Stage 4 tumours in the group of patients who had pathological correlation and who, of course, had received radiotherapy. Where CT is likely to be more accurate is in the detection of the subcategories A and B, particularly 3A and 3B, which are difficult to establish clinically. It remains to be seen whether such additional information shown by CT will lead to improved management of these tumours.

In the untreated patients CT tends to increase the stage compared with clinical examination, and from previous reports this is what one would expect if CT is being more accurate, as the clinical errors tend to be understaging (Whitmore *et al.*, 1977; van der Werf-Messing, 1978). Bimanual examination is particularly difficult in obese patients where the detection of a bladder mass may be impossible. CT is superior in defining structures in these patients because the intervening planes of fat actually help to differentiate the pelvic organs. When CT overstages, it is usually due to localised thickening of the bladder wall being interpreted as tumour invading deep muscle (Case 1). This could be the case if a superficial tumour is not removed completely at endoscopy and the thickening of the bladder wall seen on the scan is interpreted as tumour invading deep muscle. Alternatively, residual oedema of the bladder wall could similarly be interpreted as tumour mass.

Table 4

Clinical T stage	*No. of patients*	*CT staging in 27 patients after radiotherapy*		
		<3	*3*	*4*
<3	10	④	6	
3	3		②	1
4	14		3	⑪

After radiotherapy, CT relatively understages some tumours and sometimes overstages others compared with conventional staging. One of the problems of bimanual examination under anaesthesia in these patients is that post-irradiation fibrosis can anchor the bladder to the pelvic wall and thus lead to overstaging. This would exclude some patients from undergoing salvage cystectomy, a potentially curative procedure (Wallace and Bloom, 1976). CT examination of these patients may well be more accurate.

Spread of tumour posteriorly into the seminal vesicles can be accurately assessed on CT (Fig. 3), but the spread of tumour from the base of the bladder into the prostate will rarely be shown, and this appears to be an important area where CT is understaging tumours.

The findings in this series have supported other reports that CT is an accurate method of staging bladder tumours and is well tolerated by the patient (Seidelmann *et al.*, 1978; Hodson *et al.*, 1979). Seidelmann reported correct CT staging of 17 out of 21 bladder tumours, the 4 errors being due to overstaging compared with the pathological stage of the cystectomy specimens. These figures are similar to ours but gave no information on the correlation of CT and the pre-operative clinical staging. Our technique for scanning is different in that we have not found it necessary to use carbon dioxide introduced by a catheter to outline the bladder cavity. Such catheterisation makes the procedure longer and less pleasant for the patient, with the added risk of infection particularly in the radiotherapy patients. Provided the patient can tolerate a full bladder, the density of the urine outlines the inner bladder wall satisfactorily.

Data from a much larger series are required to establish whether the additional information provided by CT will produce any long-term benefit as a result of improved selection of treatment for these patients with invasive bladder tumours.

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Treatment of Infiltrating Bladder Carcinoma

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Summary—One hundred and seventy-five patients with invasive bladder tumours are reviewed.

The overall crude survival rate was 30% at 3 years and 23% at 5 years. The 5-year survival rates for T2 and T3 tumours treated by radical radiotherapy were 38% and 28% respectively.

Multiple urinary symptoms, ureteric obstruction, a large tumour, and poor differentiation were particularly unfavourable features.

The results of the treatment of non-invasive tumours of the bladder have been published (Williams *et al.*, 1977) and we now present the results in a series of 175 unselected patients with invasive tumours treated from 1967 to 1973.

Patients referred from other centres whose initial assessment was carried out elsewhere have not been included.

Patients and Methods

All patients were assessed by a full blood analysis, blood urea and electrolytes, excretory urogram and urinalysis. Lymphography was not performed.

Tumours were staged by bimanual examination under anaesthesia and the tumours were resected transurethrally for histological examination. As much of the tumour as possible was resected, except for solid, deeply infiltrating tumours, where only a biopsy was obtained. T2 lesions were categorised as those tumours exhibiting muscle invasion with no mass palpable after transurethral resection and T3 lesions were those in which a mass was still palpable. It was impossible to differentiate between T3A and T3B lesions in most instances without histological access to the whole tumour. If more patients had been treated by cystectomy it is possible that the specimen would show that some of the tumours categorised as T2 included T3A tumours. T4 lesions were those either invading the prostate or fixed to the pelvic wall. All of the histological sections were reviewed by M.A.P. using WHO classification (Mostofi *et al.*, 1973).

The age distribution is given in Figure 1, the average age being 65 years. A little over half of the patients had T2 lesions in all age groups.

Ninety-four patients had T2 lesions, 62 T3 and 19 T4.

Twenty-seven patients had no treatment apart from transurethral resection, 10 of them because the tumour was very small, was moderately differentiated and was considered to have been completely removed transurethrally. The others were considered unfit for radiotherapy.

Radical radiotherapy was either 6000 rads in 5 weeks to the bladder in patients with T2 lesions

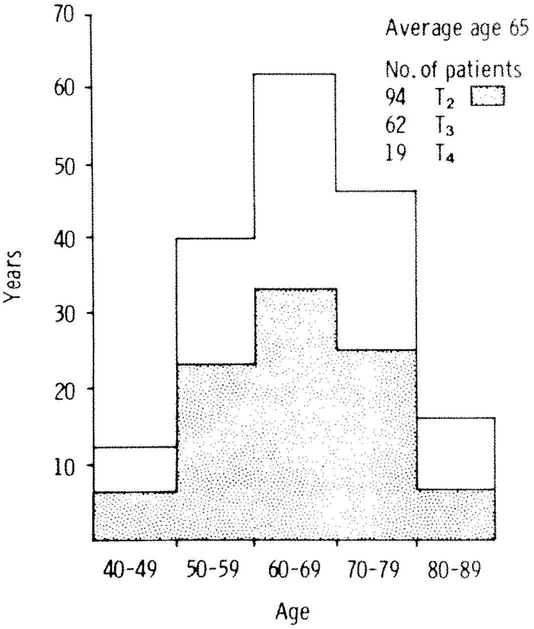

Fig. Carcinoma of bladder. Age distribution.

Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

Table 1 Carcinoma of the Bladder: Overall Results

No. of patients	*Average age*	T *Stage*	*Treatment*	*Three-year survival (%)*	*Five-year survival (%)*
34	60	T2	Radical DXR	50	38
21	63	T2	Cystectomy	57	43
29	72	T2	Palliative DXR	10	10
10	71	T2	T.U.R. only	70	60
8	72	T3	Biopsy only	17	0
17	58	T3	Radical DXR	35	28
5	65	T3	Cystectomy	20	20
32	69	T3	Palliative DXR	9	0
19	68	T4	Palliative DXR	0	0
175					

or whole pelvis radiotherapy of 5000 rads in 4 weeks for T3 lesions.

Palliative radiotherapy was either 2500 or 3500 rads in 1 or 2 weeks for T2 lesions to the bladder, or 3500 rads over 2 weeks to the whole pelvis for T3 lesions. Patients with T4 lesions had palliative radiotherapy as for the T3 lesions.

Results

The results of radiotherapy in the different groups are given in Table 1. There were 21 cystectomies in patients with T2 lesions. Three did not have any radiotherapy, but the remainder had recurrent tumours after radiotherapy. One of the 5 cystectomies in the T3 group was not given radiotherapy. Urinary diversion was by an ileal conduit. There were 5 post-operative deaths, mainly in the early years.

Table 2 Carcinoma of Bladder: Results Related to Age

Age groups	*Three-year (5-year) survival (%)*
40-49	33 (33)
50-59	31 (28)
60-69	40 (27)
70 +	18 (13)

Table 3 Carcinoma of Bladder: Results Related to Length of History

Months	*Three-year (5-year) survival (%)*
<3	36 (26)
4- 6	23 (15)
7-12	35 (35)
13-24	0 (0)
>24	13 (13)

Seven per cent of patients had a second tumour elsewhere and in 4% these tumours were the direct cause of death.

Age Groups

There was no difference in the overall survival rate in the various age groups (Table 2) except for those over 70 years.

Symptoms

Eighty-five per cent of patients presented within one year of their first symptom, 54% within 3 months and 70% within 6 months. There was no statistically significant correlation between survival and the length of history (Table 3).

In only 21% was haematuria the sole presenting symptom. In the rest, dysuria, frequency or infec-

Table 4 Carcinoma of Bladder: Survival Related to Presenting Symptoms

	Three-year (5-year) survival (%)
Haematuria only	58 (48)
Frequency/dysuria/UTI ± haematuria	23 (17)
($P < 0.002$)	

Table 5 Carcinoma of Bladder: Results Related to Urinary Infection at Presentation

	Three-year (5-year) survival (%)
Sterile	36 (26)
Infected	11 (11)
($P < 0.025$)	

Table 6 Carcinoma of Bladder: The Excretory Urogram as an Indicator of Survival

	No.	*Three-year (5-year) survival (%)*
Normal kidneys	81	41 (31)
Hydronephrosis	30	22 (19)
Non-functioning kidney	25	16 (8)
	($P < 0.025$)	

tion were associated. Those with multiple symptoms fared badly ($P < 0.002$) (Table 4). Those patients with sterile urines fared better at 3 years ($P < 0.025$) but at 5 years the differences were not significant ($P < 0.1$) (Table 5).

Patients with multiple symptoms were more likely to have large T3 tumours than those with haematuria only.

Radiography

The excretory urogram showed a tumour in 80% of cases. Ureteric obstruction was associated with a significantly poorer prognosis ($P < 0.025$) (Table 6).

Tumour Size

Eighty per cent of patients had a single tumour. Patients with tumours larger than 4 cm had significantly worse survival rates than those with tumours smaller than 4 cm ($P < 0.001$) (Table 7).

Table 7 Carcinoma of Bladder: Tumour Size in Relation to Survival

Tumour size	*Three-year (5-year) survival (%)*
0-4 cm	51 (39)
>4 cm	19 (14)
	($P < 0.001$)

Table 8 Carcinoma of Bladder: Tumour Histology

	T2, 3, 4 (%)	*T1 (%)*
Transitional	55	92
Glandular metaplasia	6	2
Squamous metaplasia	25	6
Squamous carcinoma	6	0
Adenocarcinoma	2	0
Undifferentiated	6	0

Table 9 Carcinoma of Bladder: Tumour Differentiation

	T2, 3, 4 (%)	*T1 (%)*
Well differentiated	1	69
Moderately well differentiated	36	24
Poorly differentiated	63	7

Table 10 Carcinoma of Bladder: Cellular and Nuclear Pleomorphism in Invasive and Non-invasive Tumours

	T1 (%)	*T2, 3, 4 (%)*
Low	47	0
Moderate	41	20
High	12	80

Pathology

The majority of the tumours were transitional cell carcinomas, but comparing them with our T1 series there was a greater number with squamous metaplasia (Table 8). More of the tumours in this series were poorly differentiated (Table 9) and 80% showed a high degree of cellular and nuclear pleomorphism (Table 10). Survival was not significantly influenced by the degree of pleomorphism (unlike that in our T1 series) but there was a much worse prognosis with poorly differentiated tumours (Table 11).

The overall survival rates for the different tumour stages are shown in Table 12.

Discussion

In assessing the results of therapy in invasive bladder tumours we are conscious of the difficulty in differentiating between T3A and T3B tumours. In this series it is possible that some tumours categorised as T2 would have been categorised as T3A if the whole bladder had been available for histological analysis. If this were the case then

Table 11 Carcinoma of Bladder: Tumour Differentiation Related to Survival

	No.	*Three-year (5-year) survival (%)*
Moderately differentiated	58	39 (34)
Poorly differentiated	102	24 (15)

Table 12 Carcinoma of Bladder: Overall 3-year and (5-year) Survival According to Staging

	T2	*T3*	*T4*	*All*
Number of patients	91	62	19	172
3-year (5-year) survivals (%)	43 (35)	19 (11)	0 (0)	30 (23)

the overall survival rates of those patients with T2 lesions would have been improved. It is therefore difficult to compare accurately our results with others in the literature but they are similar to those reported by Edsmyr (1975) in a series of unselected patients given radical radiotherapy, when they had a 5-year survival rate of 31% for T2 lesions and 21% for T3 tumours. Goffinet *et al.* (1975) had 5-year survival rates of 43% for patients whose tumours had superficial muscle invasion and 35% for deep muscle invasion (T3A). Their patients with (T3B) lesions had a 25% 5-year survival rate. The patients with T3 tumours who were given radical radiotherapy in the series of Wallace and Bloom (1976) had a 21% 5-year survival rate.

Our small group of patients, treated by transurethral resection only, were highly selected in that they were older, with an average age of 71 years. They also had small tumours which were only superficially infiltrating muscle, of moderate differentiation histologically, and the tumours were considered to have been completely resected.

There is a striking difference in this series of unselected patients between the survival rates of those given radical radiotherapy and those given palliative radiotherapy only. The patients given palliative treatment were the elderly and the unfit. Radical radiotherapy should certainly be given if at all possible.

Whitmore *et al.* (1977) and Wallace and Bloom (1976) have shown how combined radiotherapy and cystectomy improve the survival rates of patients with T3 tumours and high grade T2 tumours, compared with radical radiotherapy alone. Combined treatment for the patients with a low grade, superficially infiltrating tumour does not improve the survival rate when compared with radical radiotherapy alone (Whitmore *et al.*, 1977).

Lymphography is now used in selecting patients for therapy and since 1973 we have performed lymphography on all patients with invasive tumours. Patients with small, well differentiated tumours with negative lymphograms would probably do as well with radical radiotherapy alone, reserving cystectomy for those with persistent or recurrent tumours. Patients with poorly differentiated tumours, those with ureteric obstruction, and those with tumours greater than 4 cm in diameter have a poor prognosis and this is probably related to the high incidence of lymph node metastases (Whitmore *et al.*, 1977). This group of patients needs to be selected for a much more aggressive policy, *i.e.* those with negative lymphograms should have pre-operative radiotherapy and cystectomy with adjuvant chemotherapy.

Acknowledgements

We are most grateful to Professor L. Henry and Dr J. Underwood of the University Department of Pathology for advice; to Dr G. M. King of the Department of Radiotherapy, Weston Park Hospital for his advice and great help in the care of these patients; to the Medical Records Staff of the Hallamshire Hospital and Weston Park Hospital; to Mr Richard Popplewell for statistical help; to Mrs Bennett and Mrs Bridge of the Trent Regional Health Authority Health Care Team for computerising the results; to our nursing staff for their care of the patients and to the Department of Medical Photography for preparation of the tables; to Beryl Johnson, Josephine Clark and Gloria Vevers for secretarial help.

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The Pathological Anatomy of Digital Enucleation for Benign Prostatic Hyperplasia and its Application to Endoscopic Resection

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Summary—A detailed study of the macroscopic and microscopic anatomy of the prostate enlarged by benign hyperplasia and of the effects of enucleation is presented; based on this study in the cadaver, some aspects of endoscopic resection are described.

The study and its findings are described in Part I and in Part II some aspects of endoscopic resection are dealt with as 3 questions: (1) Do technical considerations allow resection of the whole adenoma without encroachment on the shell? (2) Is it desirable and feasible to attempt the resection of the glandular tissue of the shell? (3) May resection impair continence even though injury has not been caused by the cutting loop?

The discussion is concerned with 3 subjects: the morphology of the prostate, the prostatic capsule and the sphincter system.

The object of endoscopic resection for benign prostatic hyperplasia should be to achieve the same result as digital enucleation, that is to say the complete removal of the hyperplastic mass (the "adenoma") and nothing more. Digital enucleation depends almost entirely on feeling for a plane of cleavage and opening it up gently until the adenoma is removed. A knowledge of the detailed structure of the adenoma and the shell in which it lies is not essential for the successful performance of this operation. This is probably the main reason why a need has not been felt for descriptions and illustrations of the detailed anatomy of the hyperplastic prostate in the context of digital enucleation.

Randall's classic monograph (1931) on the surgical pathology of prostatic obstruction does include illustrations of the post-enucleation shell in 2 cases but without microscopy or other detail. There are, of course, many descriptions and illustrations of the anatomy (macroscopic and microscopic) of the normal prostate and it has too often been assumed that this normal anatomy could be applied to the hyperplastic gland, an erroneous view which has caused confusion. In contrast with digital enucleation, endoscopic resection depends essentially on a knowledge of the fine structure of the hyperplastic prostate, both adenoma and shell, as well as on the macroscopic pathological anatomy.

There are many excellent descriptions of endoscopic resection but they are not directly related to the model on which resection is based, namely digital enucleation. Moreover, the illustrations are for technical reasons either diagrammatic or an artist's interpretation of endoscopic findings and this has obvious limitations. Endoscopic photography has recently improved but is only just beginning to offer an objective recording. In view of these considerations it seemed that a macroscopic and microscopic post mortem study of enlarged prostates before and after digital enucleation of the adenoma would be helpful particularly to those learning the technique of endoscopic resection. A special feature of this study was to be the preservation of the pre-enucleation form of the shell by replacing the enucleated adenoma in it before fixation.

Terminology Because of its ambiguity the term "capsule" is not used except where its definition is clear. The term "shell" is used to denote the structure remaining after the adenoma has been removed. The term "adenoma" is given its common urological meaning in the context of prostatic surgery, namely to denote the compact mass of hyperplastic nodules and stroma that causes benign enlargement.

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Part 1 The Pathological Anatomy of Digital Enucleation

Materials and Methods

The series comprised a total of 20 cases. Of these, 7 were rejected, 6 because there was no prostatic enlargement or because enucleation, having been attempted, failed. One was rejected because on opening the prostatic urethra it became clear that endoscopic resection had been done in the past, a point not mentioned in the available notes.

Any male cadaver over the age of 60 was accepted provided there had been no operation on the lower urinary tract. A complete cystoprostatectomy was done and the membranous urethra was included in most cases. The bladder was then opened in the midline anteriorly and this incision was extended downwards to lay open the prostatic and membranous urethra. Enucleation was begun by placing a finger tip at one side of the verumontanum and pressing backwards (in the anatomical sense). Usually a slight pressure allowed the plane of cleavage to be entered. The lower pole of the adenoma was then mobilised. The adenoma itself was easy to mobilise but the mucosa overlying it (with the fibromuscular sheet supporting the mucosa) running downwards into the urethra (although it was easy to split vertically) usually needed to be cut across with scissors along the line marking the lower end of the adenoma if the urethra below was to be spared undue traction. If both sides of the adenoma were to be enucleated the posterior urethral wall was cut across just above the verumontanum, this incision joining the upper ends of the 2 vertical splits each side of it. The rest of the adenoma could usually be mobilised easily with the finger, but in some less advanced cases a few snips of the scissors were needed in slightly adherent areas until the mass hinged at its upper end. In some cases it was left attached like this. In others the adenoma was completely detached from the bladder neck, usually by cutting with scissors. In some cases the enucleation was confined to one side which was then left attached at its upper end. The anterior midline incision was then closed by suture but before this was done the adenoma (whether it had been completely detached or not) was replaced in the prostatic cavity so that during fixation the tissues would set in their original contours and not contract or collapse. The bladder was then packed with cotton wool soaked in formalin and the complete specimen was immersed in formalin.

Findings

Thirteen out of 20 cadavers had enucleable adenomas. Even in cases with only slight enlargement the lower poles of the adenoma could be enucleated comparatively easily. In one case enucleation was fairly easy on the left side, but on the right side after the lower pole had been freed very firm pressure was needed and suddenly the enucleating finger broke out of the original plane into a plane more peripheral, but it did not breach the outer fibromuscular layers and enucleation could be completed otherwise normally.

Macroscopic Appearances

In 2 cases the whole of the adenoma was removed and the appearance of the shell and the separated adenoma (after reconstituting the adenoma by suture of its divided anterior commissure) is shown in Figures 1 and 2. In Figure 2 the urethra has been divided immediately below the prostate. In both cases the striking thing is the position of the verumontanum. Its upper end lies above the midpoint between the bladder neck and the lower end of the cavities that had contained the lower poles of the adenoma. The verumontanum lies in the upper end of a tongue of urethral wall which is isolated by the enucleating finger as it splits the tissues vertically each side of the urethral crest in order to liberate the lower poles of the adenoma. This tongue of posterior urethral wall is demarcated above by a transverse edge made by the scissors' cut. The view of the adenoma in Figure 1, which is taken from behind and below, shows the gap which accommodated the tongue of posterior urethral wall and the verumontanum. The adenoma in both these cases weighed 18.5 g.

It will be appreciated that these photographs represent the relationships of the prostatic cavity before the adenoma was removed because the shell was held in this form by replacing the adenoma into it before the specimen was fixed. At operation on the live patient the shell contracts as the adenoma is enucleated. Also relationships are distorted in these specimens by the straightening of the natural curve of the urethra.

Microscopic Appearances

The prostate consists of numerous glands sur-

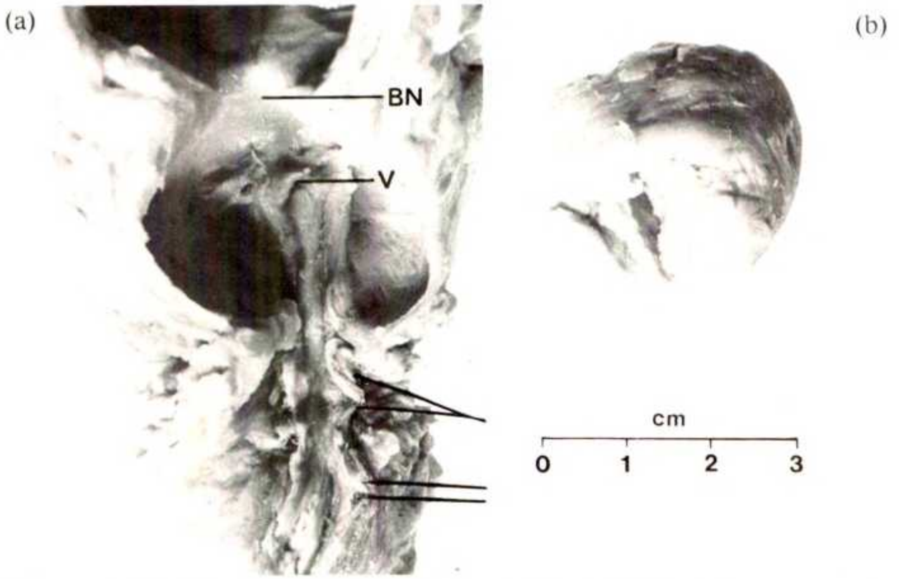

Fig. 1 Case 7. Photograph of effects of enucleation of adenoma. (a) The enucleation cavity and posterior urethra viewed from in front. BN: bladder neck. V: top of verumontanum. The anterior edge of the shell on both sides has been trimmed away so as to expose the field for the photograph. (b) Posterio-inferior view of enucleated adenoma.

rounded and separated by stroma which also covers the outer surface of the gland. The stroma is composed of smooth muscle, fibrous tissue and elastic tissue with the smooth muscle predominating.

Most of the features to be described are well demonstrated in 3 cases (Figs. 3, 4 and 5) in which enucleation was done on one side and not on the other. Transverse sections were made at about the level of the verumontanum and the adenoma has been retained *in situ.* In one case (Fig. 4) the enucleation was deliberately not completed anteriorly. In all 3 cases the plane of cleavage leaves a substantial thickness of glandular tissue in the posterior part of the shell, but the 3 cases differ from each other in the amount of glandular tissue in the lateral and anterior parts of the shell. These differences are taken to indicate progressive degrees of advancement of the hyperplastic process, which may be called degrees of maturity. The most mature case (Fig. 5) shows very little gland tissue in the anterior three-quarters of the shell, whereas in the least mature case (Fig. 3) there are gland elements in all but the anterior third of the shell.

In the adenoma the hyperplasia is essentially

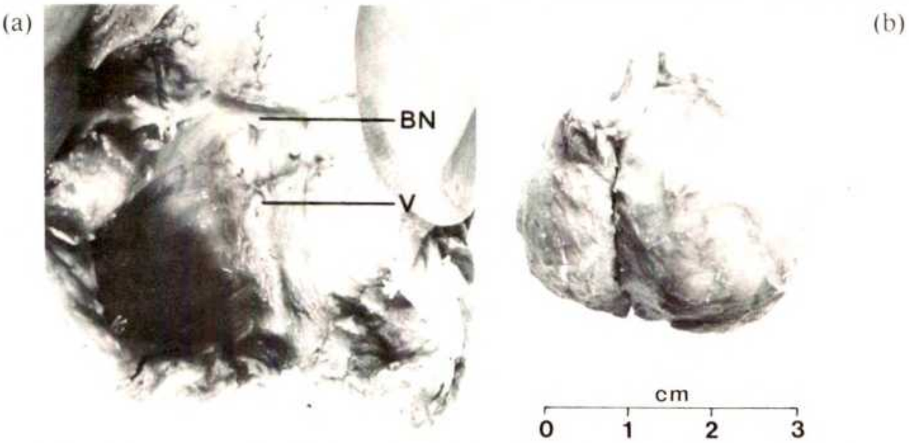

Fig. 2 Case 5. Photograph of effects of enucleation of adenoma. (a) Enucleation cavity viewed from in front. BN: bladder neck. V: top of verumontanum. (b) Anterior view of enucleated adenoma.

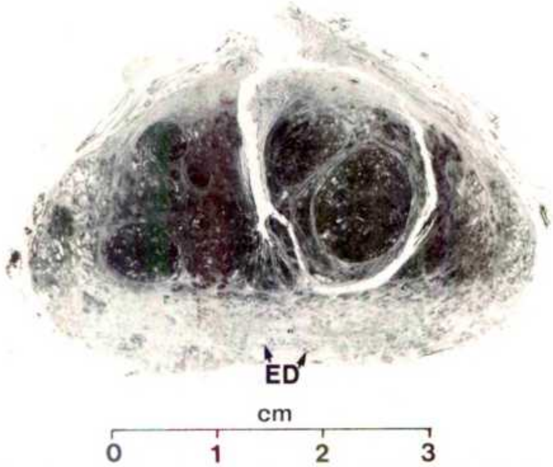

Fig. 3 Case 4. Transverse section (× 1.75) of prostate just above level of verumontanum. The adenoma has been enucleated on the right side but retained *in situ*. ED: ejaculatory ducts.

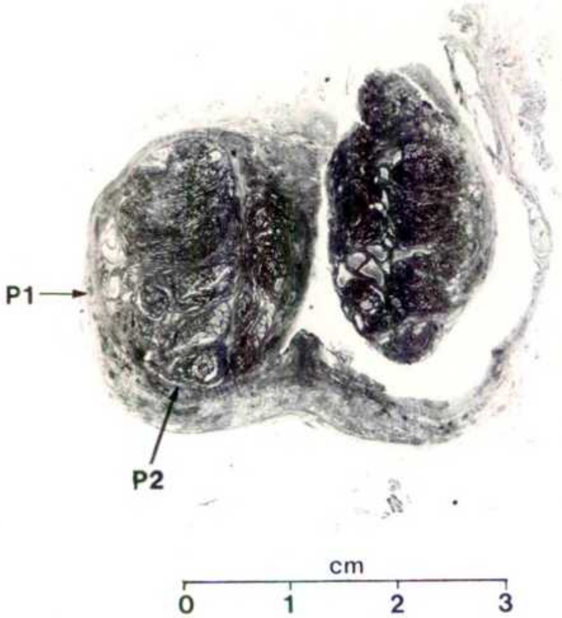

Fig. 5 Case 10. Transverse section (× 1.75) of prostate below verumontanum. The adenoma has been enucleated on the right side but retained *in situ*. P1 and P2: 2 points illustrated by magnified views in Figures 16 and 18. In the shell at 3 o'clock dilated spaces can be seen. They are lined by atrophic epithelium. On the left side a line of fibromuscular tissue can be traced continuously round the adenoma, marking it off from the shell.

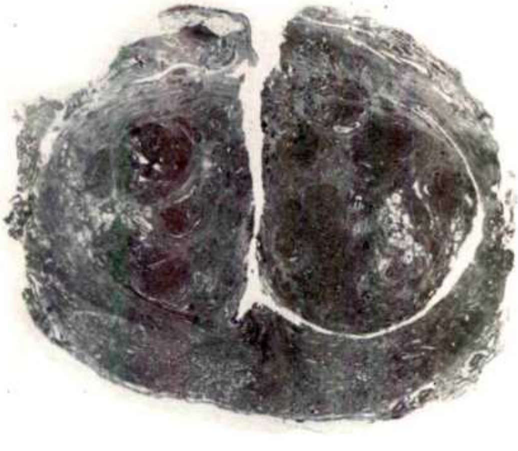

Fig. 4 Case 3. Transverse section (× 1.75) of prostate just below verumontanum. The adenoma has been enucleated on the right side but not severed from the shell anteriorly. On the left side the outline of the adenoma is clear posteriorly and anteriorly but it cannot be traced in the region round 8 o'clock.

nodular and fibroepithelial in type. Within the nodules the acini are mostly rounded and lined by tall columnar epithelium which sometimes shows papillary infoldings. Occasionally, however, they are irregularly dilated and lined by low cuboidal or flattened epithelial cells. The larger nodules are surrounded by a layer of circumferentially arranged stromal fibres which varies in thickness. In the intervening tissue the glands immediately around the nodules tend to be flattened and atrophic in appearance (Fig. 19). In some cases the entire adenoma is surrounded by a layer of condensed stroma which has a well marked fibrillary appearance (Fig. 5).

When the adenoma is surrounded by a well defined stromal layer it is within this layer that the plane of enucleation lies and in such cases the plane can easily be traced all round the adenoma on the unenucleated side (Fig. 5). In a less mature case the line may in part be missing, for example between 8 and 10 o'clock in Figure 4. In a still less mature case (Fig. 3), on the enucleated side the posterior part of the plane passes clean round a well defined nodule but as it swings anteriorly it breaks through an area of uniform gland tissue, leaving some of it in the shell and some on the adenoma. In one case (Fig. 6), referred to above in the paragraph on enucleability, the plane was very asymmetrical but no hyperplastic tissue has been left behind on either side.

In the shell the glandular tissue bordering the

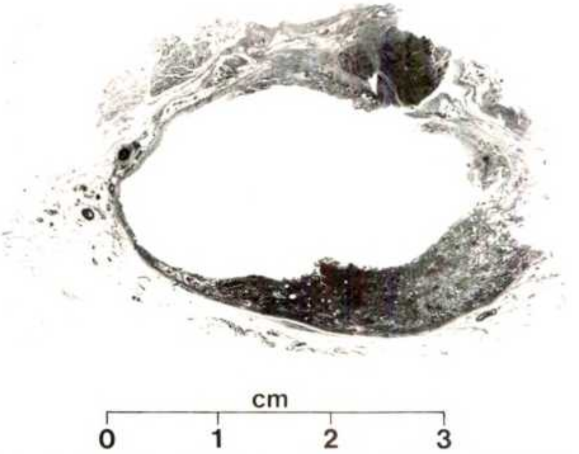

Fig. 6 Case 8. Transverse section (× 1.75) of shell below verumontanum after enucleation of whole of adenoma, showing discrepancy in thickness of shell on the 2 sides.

plane of enucleation is relatively flattened and atrophic as if compressed by the adenoma (Fig. 7). Where the shell is very thin it may contain no glands at all or merely a few slits or quite large spaces lined by flattened epithelial cells (Fig. 5). In the posterior part of the shell (where there is always glandular tissue) the epithelium is usually, but not uniformly, atrophic, even though the acini may not be flattened. There are places in which dilated atrophic glands on one side of the enucleation plane may be indistinguishable from those on the other side of the plane (Fig. 8).

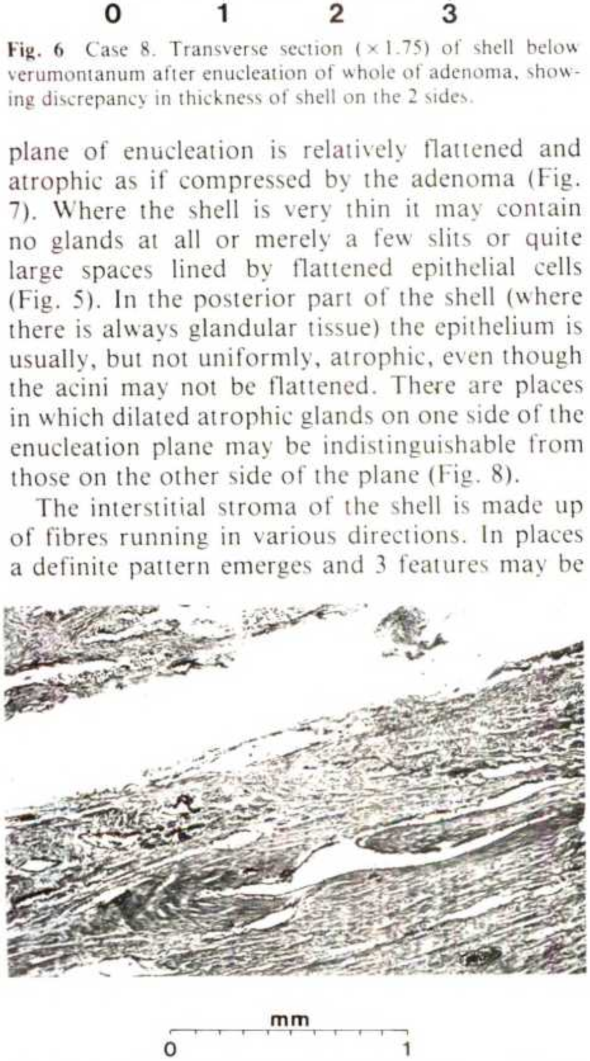

Fig. 7 Case 3. Photomicrograph (× 16) of transverse section through plane of enucleation (5 o'clock in Fig. 4) showing compressed glandular tissue in shell.

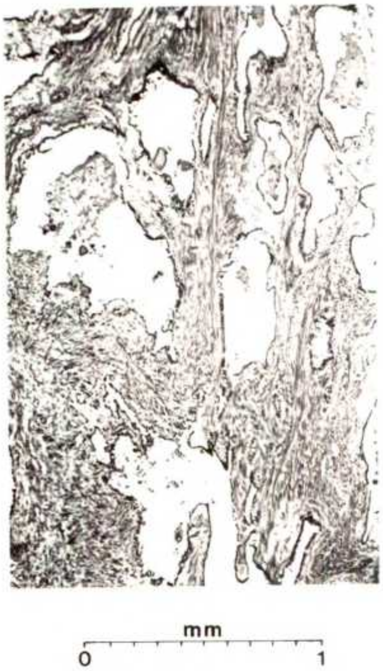

Fig. 8 Case 3. Photomicrograph (× 16) of transverse section (at 8 o'clock in Fig. 4) showing similar tissue (dilated spaces with atrophic epithelial lining) on both sides of plane of cleavage.

The interstitial stroma of the shell is made up of fibres running in various directions. In places a definite pattern emerges and 3 features may be described. The first is a layer of stroma lining the shell. It constitutes the peripheral part of the layer through which the plane of enucleation passes. This lining often has gaps in it where glandular tissue lies uncovered. The second feature is a relatively thick septum that lies near the midline posteriorly where the fibres run transversely and seem to mark the posterior limit of the enucleation plane (Fig. 12). If this layer is followed laterally it is seen to contribute to the lining of the shell. Thirdly, within the posterior part of the shell generally there are transversely running stromal fibres which, if followed laterally between the gland elements, are seen to converge on each other as the gland tissue tapers off and they join with the outermost layers of the stroma to form a composite fibromuscular layer (Fig. 11). At its point of formation this layer may be as much as 3 mm thick but it rapidly attenuates as it runs forward over the sides of the adenoma, constituting that part of the shell which contains only fibromuscular tissue.

On the posterior part of the prostate (composed of original, non-hyperplastic tissue) the external covering of stroma appears no different from the interstitial stroma. It is shown in Figure

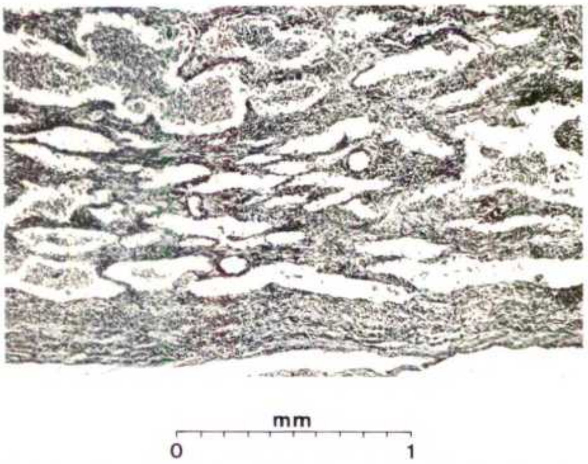

Fig. 9 Case 10. Photomicrography (× 16) of posterior part of shell showing on its periphery (lower edge) the anatomical "true" capsule.

9 and here it is 0.25 mm thick. In cases 3 and 4 this thickness was 0.5 mm or less at most of the points measured and in some places as little as 0.1 mm. This is the anatomical "true capsule" (Glenister, 1976).

The Distal Part of the Shell and the Prostatic Urethra

In case No. 7 (Fig. 1) the entire specimen was embedded in celloidin to preserve its shape and it was then cut transversely at 3 levels which are indicated in Figure 10. The resulting microscopic sections are of necessity thicker than those that would have been produced by embedding in paraffin. The top level (Fig. 11), just above the verumontanum (the ejaculatory ducts are nearer the anterior than the posterior surface of the shell), shows that the shell is of substantial thickness posterolaterally because of its content of gland tissue. The shell is lined by stromal fibres. The next section (Fig. 12), which cuts through the point midway between the verumontanum and the lower end of the enucleation cavity, shows in general a similar glandular and stromal pattern to that of Figure 11 except for a concentration of glandular tissue astride the midline near the periphery of the shell. The distinctive feature of this section is the urethral crest with its keel of longitudinal smooth muscle fibres (Fig. 13) measuring 4 by 0.8 mm. In the most distal section (Fig. 14) there are few glandular acini near the urethral lumen and in the intermediate zone, but there is a cluster (2.5 × 7 mm) near the periphery astride the midline. The urethral crest is still prominent but flatter and broader. Its muscle keel measures 2.2 × 1.1 mm. Immediately

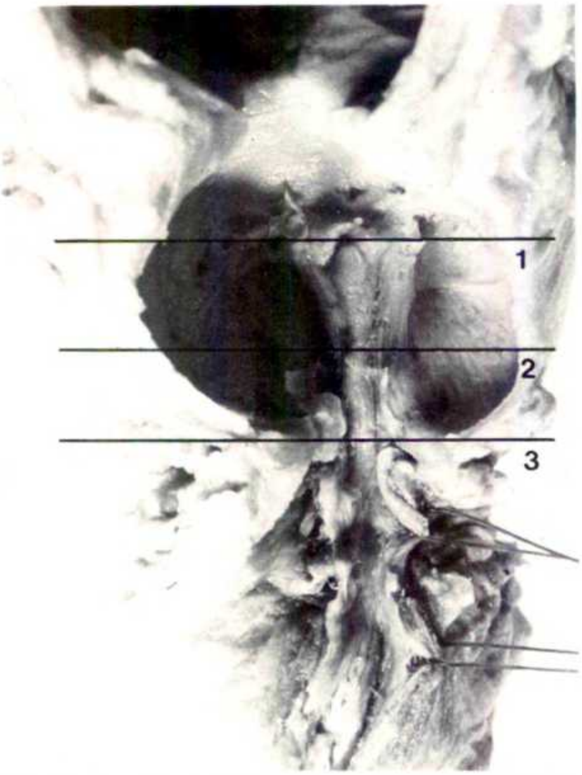

Fig. 10 Case 7. Photograph of shell (as in Fig. 1) showing levels of transverse sections represented in Figures 11, 12 and 14.

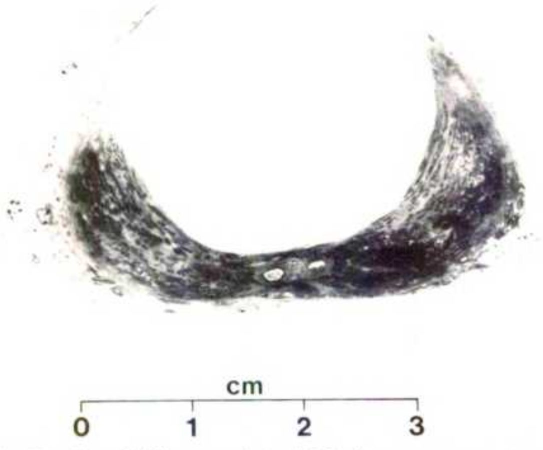

Fig. 11 Case 7. Photograph (× 1.75) of transverse section of post-enucleation shell above verumontanum (level 1 in Fig. 10). The ejaculatory ducts are clearly seen. If the stromal fibres are followed through the glandular tissue they can be seen to converge and to form the anterior part of the shell where it consists only of fibromuscular tissue.

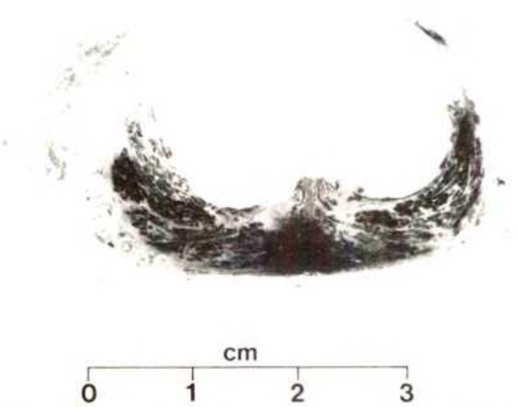

Fig. 12 Case 7. Photograph (× 1.75) of transverse section of post-enucleation shell midway between top of verumontanum and lower end of enucleation cavity (see Fig. 10). Running laterally on each side from the base of the urethral crest is a broad band of stromal tissue from which septa pass among the gland elements and also contribute to the lining of the shell.

posterior (peripheral) to the keel is a concentrated circular band of smooth muscle. Encircling this is a wider but less compact band of smooth muscle and among its fibres lie the glandular elements mentioned above. Anteriorly, numerous striped muscle fibres mingle with the more peripheral smooth muscle fibres. The total thickness of smooth muscle (including the gland elements lying in its interstices) which surrounds the urethral lumen and the urethral crest is 6 mm. The extrinsic striped muscle sphincter could not be preserved in the specimens of this series because the prostate and urethra below it had to be detached from the pubic arch and consequently the periurethral soft tissues collapsed. In most specimens, intrinsic striped muscle fibres were quite conspicuous, especially in the anterior part of the prostate and even in the anterior part of the enucleated adenoma. These fibres represent Henle's muscle (Manley, 1966).

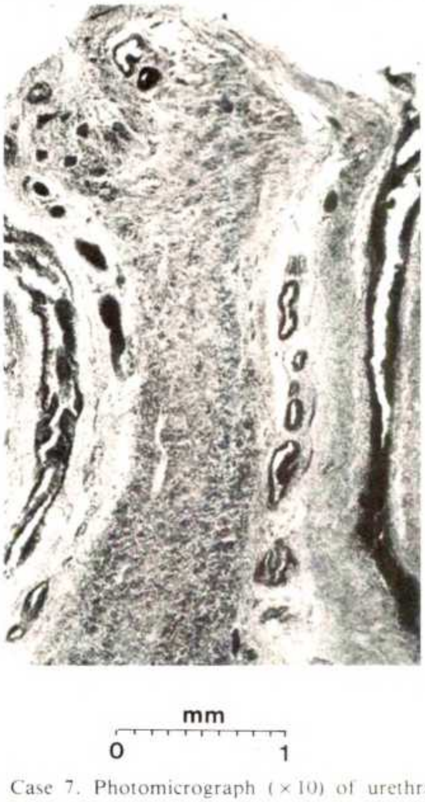

Fig. 13 Case 7. Photomicrograph (× 10) of urethral crest showing midline keel of longitudinal smooth muscle fibres. Same level as Figure 12.

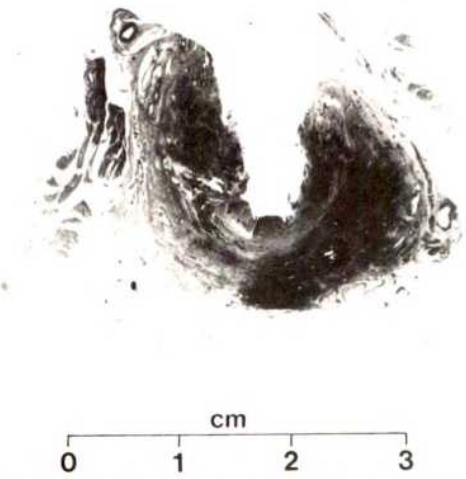

Fig. 14 Case 7. Photograph (× 1.75) of shell at level of lower end of enucleation cavity (see Fig. 10). The urethral crest is broader and flatter than in Figure 12 and its base rests on a compact band of circular smooth muscle (prostatic lissosphincter). Peripheral to this is a broader band of tissue comprising glandular elements and more loosely packed muscle fibres.

Structures in the Periphery of the Shell

Immediately peripheral to the outermost layer of fibromuscular tissue are found loose areolar tissue, fat, veins and arteries (Fig. 15). There are also the fibres of the visceral layer of the pelvic fascia in more or less close contact with the outer surface of the prostate. This is the anatomical false capsule (Glenister, 1976). The fat occurs in small patches often closely applied to the fibromuscular coat and sometimes actually within its substance. It is composed of globules

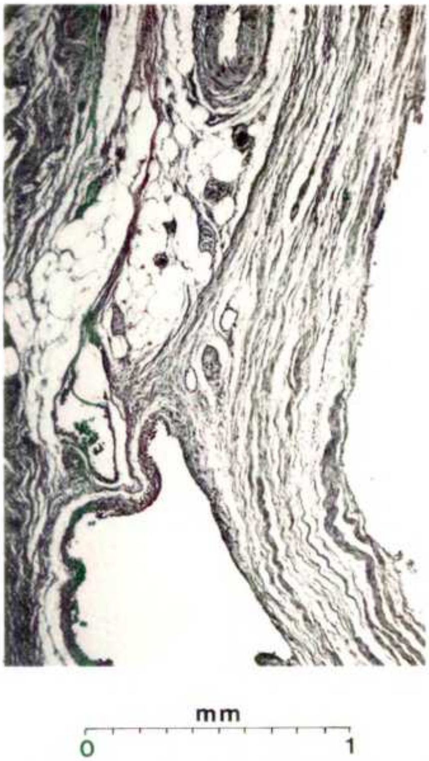

Fig. 15 Case 8. Photomicrograph (× 16) of part of section illustrated in Figure 6 (at 9 o'clock) showing the fibromuscular post-enucleation shell (right) and immediately outside it part of lumen of vein (lower end of field), and area of fat globules (mid-field) and an arteriole (upper end of field).

about 0.05 mm in diameter. Veins are seen in every section. They are often in immediate contact with the outer fibromuscular layer and are often large, covering a considerable area of the prostatic surface. On the left side of the section shown in Figure 5 a vein can be traced for 3 cm.

Part 2 Endoscopic Resection

Three questions arise out of the findings which have been described in Part 1.

1. Do Technical Considerations Allow the Resection of the Whole Adenoma Without Encroachment on the Shell?

If endoscopic resection is to reproduce exactly the effects of enucleation it must be possible to identify visually the limits of the adenoma. These limits are usually marked by a fibromuscular layer and when this layer completely surrounds the adenoma (as in Figure 5) it might be thought that the limits of the adenoma could be established by identifying this layer, commonly called the surgical capsule (Semple, 1963). This term will be used in this sense only. In considering to what extent the surgical capsule can be identified and so used to mark the limit of resection some basic details need to be examined.

(*a*) The resectoscope loop is made of wire about 0.3 mm thick. Because it is curved it cuts a groove of rounded section and not a flat-bottomed trench. This groove has to be at least 1 mm deep in its midline before its width is 75% of the maximum width of which the loop is capable. The loop has to sink in 4 mm before its maximum width is brought to bear.

(*b*) For the identification of tissue an adequate extent of its cut surface must be displayed.

(*c*) It may be said that any layer of tissue must have a groove about 1 mm deep cut into it before it can be identified. This means that layers less than 1 mm thick probably cannot be identified because their whole thickness will have been resected before their texture has been adequately displayed. It also suggests that slightly thicker layers (say up to 2 mm thick) will be considerably weakened or even disrupted before their normal texture is displayed. This applies particularly where the surgical capsule constitutes the outermost layer of the prostate because here it lacks any support on its outer surface.

(*d*) At any one point the surgical capsule constitutes either (i) the outer surface of the prostate or (ii) a septum intervening between the adenoma and the residual prostatic glandular tissue. In most cases the first relationship applies to the anterolateral part of the enlarged prostate. The second relationship applies in every case to the posterior part of the prostate and in a very immature case it may extend far anteriorly. These 2 relationships lead to 2 different sets of problems for the resector.

(*e*) In so far as the resector is guided by the appearance of the cut surface of the tissue he can never know for certain what he is about to cut, but only what he has already cut. In practice, circumstantial evidence often provides varying degrees of probability as to the outcome of the next cut, but probability is not good enough if a precise dissection is to be achieved.

(*f*) If resection is being directed laterally towards the point P1 in Figure 5 where the surgical capsule is only 0.25 mm thick (Fig. 16) it is virtually certain that the resector, when he reaches the periphery of the adenoma, will see in 2 consecutive cuts glandular tissue and then the

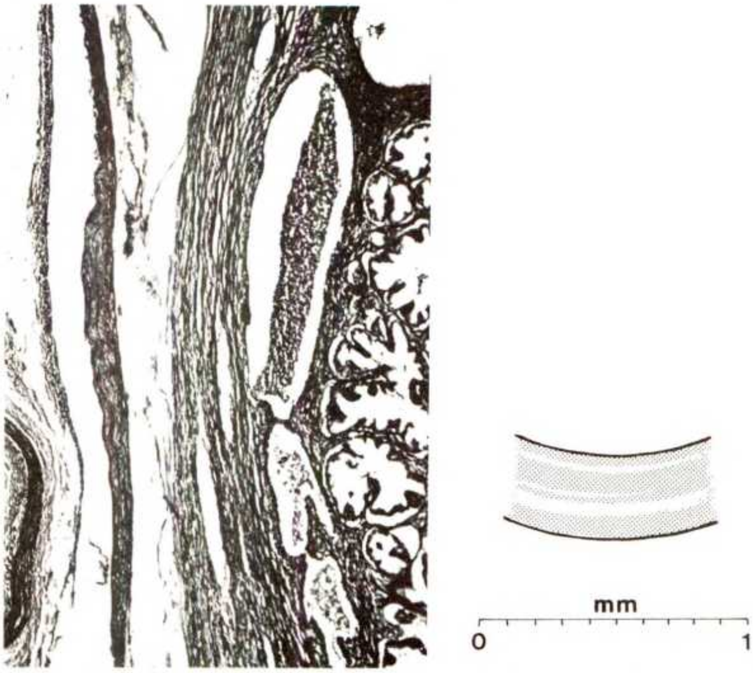

Fig. 16 Case 10. Photomicrograph (× 16) of part of section illustrated in Figure 5 (P1) showing edge of hyperplastic nodule (right) bordered by the surgical capsule. Outside the capsule is a length of vein. Also represented is part of resectoscope loop wire to same scale.

classical evidence of a "breach of the capsule". The various manifestations of such a breach have been well described but one of them is of special note as it is so characteristic, namely the appearance of the periprostatic fat (Fig. 15). The microscopic structure of this fat is clearly reflected in its endoscopic appearance. The pale yellow fat brightly reflects the light and the tiny globules give a characteristic finely granular texture.

The breach of the capsule might still have been caused if the surgical capsule had been much thicker, say 2 mm, and the resector had been cutting pieces 2 or 3 mm thick and had made his penultimate cut immediately short of the periphery of the adenoma, but if his penultimate cut had been 1 or 2 mm short of the periphery he might with his next cut lay bare the substance of the capsule without actually causing a breach. He might then see the conventional endoscopic picture of the capsule, a fairly coarse network of glistening fibres. The microscopic picture of this tissue (Fig. 17) shows a close texture of fine bundles rather different from the relatively coarse network depicted in the conventional illustrations of the capsule. This suggests that the standard endoscopic picture is a view of the capsule slightly disrupted. It is certainly true that in practice such a picture may quite quickly change to one of an obvious breach without any further cutting having been done.

(*g*) If resection is directed towards that part of the shell containing glandular tissue (P2 in Fig. 5), the surgical capsule presents a different problem to the resector (Fig. 18). The thinness of this layer (it is here about 0.3 mm thick) makes it extremely likely that it will escape identification, and in this situation there will be no unequivocal circumstantial evidence that its line has been crossed, unlike what happens when the outer surface of the prostate has been breached. Immediately before this line was crossed the resector was looking at the typical picture of cut glandular tissue. The next cut (which will have removed or destroyed the thin layer of surgical capsule) will also reveal glandular tissue. This will be the glandular tissue of the shell. It is true that under the microscope this rather atrophic tissue is usually easy to distinguish from the tissue of a hyperplastic nodule. On the other hand, within the adenoma, between the hyperplastic nodules, there is some atrophic glandular tissue, so that this type of tissue is not the hallmark of "shell". For example, Figure 8 shows atrophic flattened gland

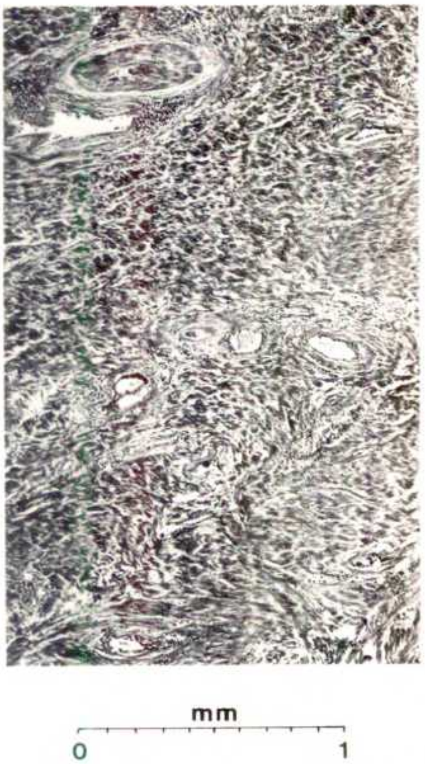

Fig. 17 Case 10. Photomicrograph (×16) of section of surgical capsule taken in the plane of resection. The section is from the anterior half of the unenucleated side of the prostate above the level of the section shown in Figure 5. It shows the close texture of the tissue even at this magnification.

elements lying on both sides of the plane of cleavage. If the microscope cannot with certainty allocate a fragment of tissue as between the adenoma and the shell, how much more difficult for the resector to do this. No less an expert than Barnes (Barnes *et al.*, 1959) admits the difficulty of distinguishing compressed glandular tissue from adenoma. Therefore if the resector (who has crossed the point P2 in Fig. 5) is seeking the periphery of the glandular mass he will continue to resect the shell until he reaches the anatomical true capsule. The signal for his arrival here is almost certain to be a breach of this tenuous structure. In resecting the glandular tissue of the shell he will also have resected the smooth muscle septa on which the contractility of the shell depends.

(*h*) The fibromuscular septa within the adenoma may be considerably thicker than the surgical capsule (Fig. 19). Therefore it does not follow that the identification of a fibromuscular layer is the identification of the surgical capsule.

All of these considerations lead to the conclusion that the identification of the surgical capsule without breaching it is always difficult and often impossible. There is a good case for modifying the resectionist's slogan "Down to the capsule!" More than 25 years ago Nesbit was advocating such a policy and used to quote a saying to the effect that urologists spent their first years learning how to resect down to the capsule and the rest of their time learning how to stop short of it. The same policy has been implied by various writers since then but ill defined uses of the term "capsule" have led to some confusion and ambiguity. In particular, the term "compression capsule" has implied that it is possible to resect the entire adenoma and still leave a

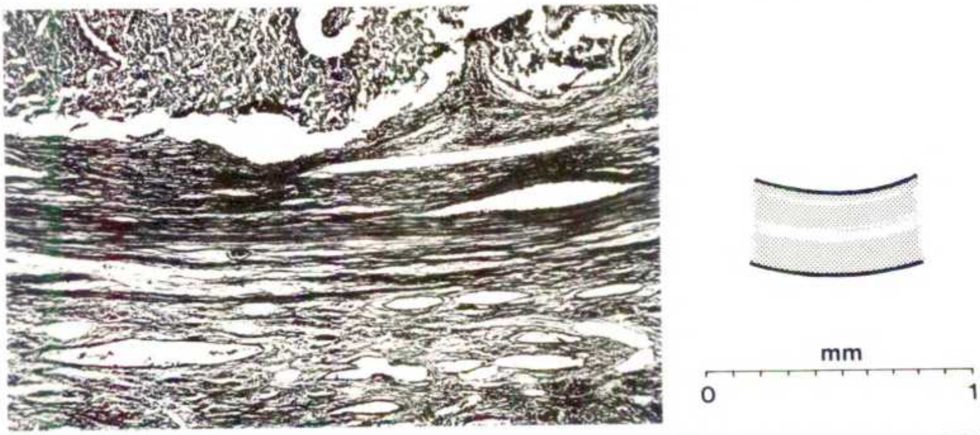

Fig. 18 Case 10. Photomicrograph (×16) of part of section illustrated in Figure 5 (P2) showing in upper part of field the edge of a hyperplastic nodule, in the lower part of the field the glandular tissue of the shell (with compression changes) and, separating the 2, the surgical capsule. Also represented is part of resectoscope loop wire to same scale.

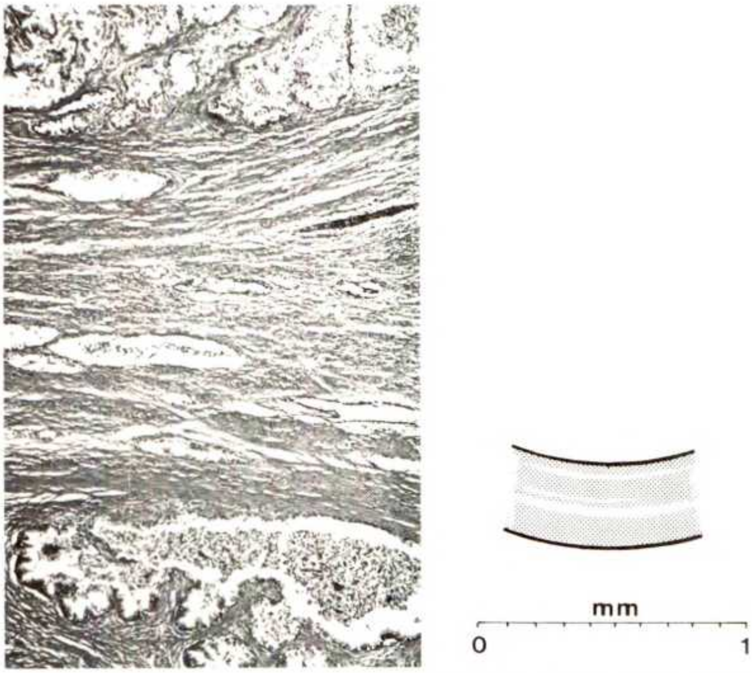

Fig. 19 Case 4. Photomicrograph (× 16) of part of adenoma (right side of Fig. 3) showing relatively broad septum of fibromuscular tissue between 2 hyperplastic nodules. The septum contains elongated spaces which are the remains of compressed gland elements. They are lined by atrophic epithelium.

complete layer of glandular tissue (albeit compressed glandular tissue) lining the shell. In 3 cases of the present series (nos. 5, 7 and 10) at least half of the shell was devoid of glandular tissue. It follows that in such cases a complete lining of glandular issue ("protecting" the outermost fibromuscular layer of the prostate) could only be achieved by leaving a layer of adenoma in those parts of the shell. This policy is unequivocally accepted by Conger (1963) who writes "It is not the purpose of the operator to expose the capsule completely. . . . It should be remembered that a thin layer of prostatic adenoma lying over the capsule will not interfere with urination. . . . There should however be no large projections of devascularised tissue."

This last point raised by Conger leads to a consideration of the lower poles of the adenoma, as their arterial supply comes down from above through the urethral branches which are usually divided when the upper part of the adenoma is being resected. It is therefore necessary to resect the lower poles of the adenoma because they will have been devascularised. The lower poles often descend below the level of the verumontanum (Figs. 1 and 2), but the conventional warning is never to resect below this level, although Barnes (1943), Nesbit (1951), Thompson (1953) and Mauermayer (1962) have all qualified this warning. There is no doubt that resection in this region requires very special care on account of the danger of injury to any of the components of the distal sphincter mechanism. Nevertheless, a study of the enucleated adenoma and the shell, and the correlation of these with the endoscopic view of the lower poles, are reassuring. There are good landmarks. Looked at from below, the demarcation between the bald bulge of the adenoma with its tight mucosal covering and the rather corrugated urethral wall below with its mobile mucosa presents a characteristic picture. Often a distinct curved line can be discerned here, marking the junction. This may become clearer as resection proceeds. When the lower pole is being excavated from above and its mucosal covering begins to lose the support of the glandular substance behind it, becoming more pliable, it may accentuate the demarcation line by bending as if on a hinge at that level. In contrast to the prostate above it, the shell round the lower poles of the adenoma has changed from a predominantly glandular structure into a predominantly muscular tube in which the prostatic lisso-sphincter lies very near the urethral lumen (contrast Fig. 12 with Fig. 14). In this apical region no risks may be taken and it is right to leave a layer of glandular tissue even if it is part of the adenoma. Although the main arterial supply of the apical tissue will have been interrupted in the resection of the upper part of the adenoma, the peripheral layers of the adenoma are supplied direct by capsular arteries (Flocks, 1943) so that residual tissue will not be ischaemic unless it is bulky.

A bulky residuum is most undesirable and can usually be avoided by the following measures. 1. The assessment of the prostatic bulk using bimanual (rectal and abdominal) palpation. 2. The building up of a stereoscopic visual image of the interior (luminal) conformation and limits of the adenoma before resection starts. It must be remembered that the shell after resection will not be the same as when it was filled out by the intact adenoma. It is a contractile structure and closes down as the adenoma is resected. 3. A bulky residuum will usually show itself as an intraluminal projection having the texture of glandular tissue. 4. Rectal palpation towards the end of resection may be helpful but it will not distinguish between residual adenoma and a thick shell.

2. *Is it Desirable and Feasible to Attempt the Resection of the Glandular Tissue of the Shell?*

An obvious reservation about enucleation arises from the residual glandular tissue in the shell because of its bearing on the question of recurrence of hyperplasia and the development of carcinoma. As for carcinoma, it is now generally accepted that it arises mostly in the peripheral zone of the true prostatic tissue. This zone is not only peripheral to the central zone, it is also distal to it. The relation between the 2 zones is rather like an inverted cone fitting into a funnel below it (O'Donoghue and Pugh, 1977). The peripheral zone extends downwards behind the prostatic urethra right into the distal sphincter system. If an attempt were made by endoscopic resection it would be possible to remove a great deal of the glandular tissue of the shell, but this would entail an extensive exposure of the outer fibromuscular layer of the shell which would carry a high risk of its injury and perforation. Such injury in its lower part would greatly endanger the smooth muscle sphincter system. If an attempt were made to burrow behind the prostatic urethra to resect the distal extension of the peripheral zone in the midline below the verumontanum, incontinence would be almost certain, due to injury of the smooth muscle sphincter and the accessory continence factors in the submucous region.

The problem of recurrence of hyperplasia raises different considerations. For one thing it is uncommon, or rather symptoms due to it are uncommon. This may be because of the long interval between the operation and the recurrence of symptoms. In a recent report (Steg and Aboulker, 1976) of 21 cases the interval was less than 10 years in only one case and over 15 in 7, including 2 cases with an interval of over 20 years. Insufficient is known about the origin of recurrent hyperplasia to set a specific target for its prevention. It may even be that hyperplasia starts not in the glandular tissue but in the stroma. There is not a good case for extending a satisfactory operation in an attempt to prevent a benign condition from recurring, especially if the aetiology has not been soundly established and if the recurrence of symptoms is known to be infrequent and long delayed. It might be argued that as the hyperplasia probably originated in the upper part of the prostate there would be no need to resect its lower part to prevent recurrence. Clearing the glandular tissue from the upper part of the shell would be unlikely to cause incontinence even if the shell were breached. Nevertheless, the penalties that might have to be paid for a breach of the shell even at this level are extravasation (seldom serious), venous bleeding (sometimes very troublesome) and intravenous transfer of irrigant (probably uncommon but sometimes extremely serious). On balance there is no good case to be made for resection of the glandular tissue of the shell.

3. *May Continence be Impaired Without Injury by the Cutting Loop?*

Incontinence following endoscopic resection is usually assumed to be due to injury by the cutting loop, but perhaps the resectoscope may cause damage in another way. It may be that one of the factors in continence is the softness and suppleness of the mucosal and submucosal tissues and in particular the urethral crest. The sheath of the resectoscope must press on the urethral crest for the entire duration of the operation and particularly so if the sheath is too large to lie easily in the urethra. The effects of prolonged pressure on a delicate structure might result in subsequent scarring and shrinkage. Consequently the urethral crest might become ineffective as a plug due to atrophy and sclerosis. It seems possible that some of the minor degrees of incontinence following resection might be due to this sort of cause. Blandy (1978) has made an observation that may be relevant to this question. In 2 cases investigated for impaired continence after resection, endoscopy showed an unusually smooth or flat appearance of the mucosa of the prostatic urethra and no other abnormality.

Discussion

A correct concept of the anatomical objectives of prostatectomy depends on a knowledge of the process of prostatic enlargement and of the morphology of the prostate, which to some extent determines what form the enlargement will take. A clear appreciation of what is removed by enucleation and what is retained has been hindered by confusion due to varying uses of the term "prostatic capsule". To ensure that prostatectomy does not impair urinary continence it is necessary to know the points at which the sphincter system is particularly at risk. The findings in this study provide a basis on which to consider these matters.

The Morphology of the Prostate

For many years the prostate was considered to have a lobar structure. According to Lowsley (1938) there were 2 lateral lobes, a posterior lobe and a middle lobe. A modern view rejects this and substitutes a structure of concentric zones. Franks (1954) raised the issue in a general sense and McNeal (1968) has worked out a system in detail, a system that is generally welcome as better fitting the facts. It is difficult to escape the conclusion that the old concept arose from a confusion between the anatomy of the truly normal prostate and the prostate involved by hyperplastic changes. These changes do indeed lead to the formation of a strikingly lobar structure. This lobar structure came to be regarded as the prostate and its removal by operation as prostatectomy. Freyer (1901) went so far as to write of his operation as "total extirpation of the prostate", but according to McNeal the hyperplastic changes arise in urethral glands which are not a part of the prostate. This view changes the concept of prostatectomy. If taken to its logical conclusion it completely eliminates it when it is applied to the enucleation of the adenoma. It does not simply deny Freyer's claim that he removed the whole prostate. It asserts that he did not remove any of it. The modern term adenomectomy instead of prostatectomy is correct but it has not gained wide currency.

The post-enucleation shell may be regarded as the entire prostate, including both the central and the peripheral zones of McNeal, which has been expanded and distorted by the mass of hyperplastic tissue that has formed within it. The middle and lateral lobes of the "enlarged prostate" are simply conformations of extraneous pathological tissue. The specimens illustrated in Figures 1 and 2 show rather strikingly how the lower poles of the lateral lobes of the adenoma project well downwards below the level of the verumontanum. This relationship is also shown in the 2 illustrations of the post-enucleation shell in Randall's monograph (Randall, 1931). The hyperplastic tissue originates in the urethral glands above the level of the verumontanum. The fact that it pushes downwards from above is attested by 2 common findings at the enucleation operation. Firstly, the main blood supply enters the adenoma near its upper end. This is obvious to the operator both in open and endoscopic prostatectomy. Secondly, in digital enucleation the part of the adenoma that separates most easily from the shell is the lower pole. This was quite striking in the post mortem enucleations. Flocks' account (Flocks, 1943) of the blood supply of the enlarged prostate accords with this, and more recent support is provided by some French workers (Duclos *et al.*, 1972).

The Prostatic Capsule

The use of the term "prostatic capsule" is often confusing. It has been defined in various ways and it is sometimes used without clear definition. Anatomists (Glenister, 1976) now apply the term to 2 things. One is the condensed pelvic fascia around the prostate, the anatomical "false capsule". The other, the anatomical "true capsule" is described as a "thin firm condensation of fibrous tissue" at the periphery of the prostate which is "firmly adherent to the prostate and is structurally continuous with the stroma of the gland". The findings in the present study do not falsify this account but do suggest a rather different emphasis. From the urologist's point of view it might be said that to single out the peripheral layer of the fibromuscular stroma and to give it a special name ("capsule") was to elevate it to a status it did not deserve. The resector might also be unwilling to concede the epithet "firm" as a description of this layer. Of all the tissues he encounters it is perhaps the most fragile.

The standard anatomical description of the capsule applies to the normal prostate. The advent of hyperplasia changes things greatly and 4 terms have been applied by urologists to the resultant pathological anatomy. These terms are "surgical capsule", "false capsule", "compression capsule" and "true capsule". To some extent the first 3 terms are interchangeable. According to Barnes *et al.* (1959) "The false or surgical capsule . . . is prostatic tissue compressed against the true capsule by the adenoma and is difficult to differentiate from adenomatous tissue." Barnes implies that this capsule contains gland tissue recognisable through the resectoscope. Nesbit (1947) writes: "The appearance of the compression capsule is different from either the normal or the adenomatous prostate gland: it has a sort of asbestos appearance when viewed through the foroblique system." It is clear that both Barnes and Nesbit are referring to the same structure, so that for them the terms "surgical capsule", "false capsule" and "compression capsule" all refer to parts of the shell still retaining glandular tissue. Semple (1963), reporting on a post mortem study of the prostate in which he made transverse sections for microscopy, wrote "The term 'surgical capsule' is applied to the fibromuscular covering of the hypertrophied lobes of the benign enlargement of the prostate; it separates the hypertrophied peri-urethral glands from the glands of the posterior lobe." (It should be noted that the old and unsatisfactory term "posterior lobe" refers to what remains of the normal prostate, that which is called the shell in this study.) It is clear that Semple's use of the term "false capsule" is more restricted than that of Barnes and Nesbit. Barnes uses the term "true capsule" in a way that suggests that he is referring to the whole thickness of the shell where it consists only of fibromuscular tissue (the original glandular elements having atrophied), something more substantial than the exiguous anatomical true capsule. In this study the term "surgical capsule" is used in Semple's sense.

The Sphincter System

The urethral sphincter system is a complex and controversial topic. In this paper a deliberately restricted view of the subject is taken, based on the assumption that complete enucleation of the adenoma, properly performed, leaves the urinary sphincter mechanism intact. The phrase "properly performed" is taken to mean that enucleation is done gently and carefully in such a way as not to injure the shell or the wall of the urethra below the verumontanum. This implies that the case is suitable for the operation, particularly in having a complete plane of enucleation. After such an operation the return of complete urinary continence is taken for granted, and it follows that none of the tissues removed with the adenoma was essential for urinary continence. The smooth muscle inevitably removed during enucleation probably includes the pre-prostatic sphincter (McNeal, 1972). It may be that this structure is concerned more with preventing reflux of semen than efflux of urine. The next point to make is that most of the detailed anatomical studies of the urethral sphincter system have been made on subjects with normal prostates. It is not easy to apply these findings to the prostate enlarged and distorted by hyperplasia.

At birth the prostate consists mainly of smooth muscle with a comparatively sparse peppering of glandular elements mainly in its posterior part. It is a muscular tube continuous with the urethra below it. The presumption is that all of its muscle functions effectively. When it becomes further invaded by glandular elements (as happens shortly after birth and much more extensively after puberty) we may assume that the muscle fibres, now thickly interspersed with gland elements, continue to subserve their original function (Scher, 1950). Some observers (Lapides, 1958; Davis *et al.*, 1961) regard urinary control as being due to the total action of the tube of smooth muscle comprising the prostate and posterior urethra. Post-prostatectomy incontinence is due to injury to this muscle system (Thomson, 1961). Tanagho and Miller (1973) have also stressed that encroachment "outside the adenoma" may destroy the smooth muscle sphincteric system at various levels. The 3 levels they specify are: "at the internal meatus", in the compressed prostatic capsule and at the apex of the prostate below the level of the verumontanum. Elliott (1954) has stressed the importance of the circular smooth muscle at this last site. It is also described by Hayek (1969) who calls it the prostatic lissosphincter. It is shown in Figure 14. The action of this muscle is reinforced in certain circumstances by the (voluntary striped muscle) extrinsic sphincter but is not constantly dependent on it (Lapides *et al.*, 1960).

The cases in the present series show how the smooth muscle elements of the stroma persist when the glandular elements in the shell have atrophied and so presumably continue to exert a sphincteric action. There is, however, good clinical evidence that normal urinary control can be maintained when the function of the upper part of this smooth muscle system is impaired. Urethrographic studies of patients after prostatectomy (Caine and Edwards, 1958; Whitaker, 1971) have shown that it is common for the prostatic cavity to be incapable of emptying itself. Caine and Edwards showed that when a normal patient interrupted his urinary stream the urethra was immediately shut off at the external sphincter and then the urethra above that level closed progressively from below upwards until it was entirely empty, and they illustrated one post-prostatectomy case with the same capability. In most post-prostatectomy cases the same shutting-off process started but the upward emptying stopped at the lower end of the prostatic cavity, leaving the cavity permanently open. It therefore appears that after prostatectomy the muscle in the shell may not be capable of emptying the cavity. Although this by itself does not result in any disability, it should be accepted that the loss of some of the effective length of the sphincteric tube may reduce the margin of safety of the remaining (lower) part of the system, so that operative injury to this lower part might more easily cause incontinence. This problem of a dual weakening of the sphincteric system is discussed by Turner-Warwick *et al.* (1973) in the context of trans-sphincteric urethroplasty combined with prostatectomy or any operation on the bladder neck.

In addition to muscle, elastic tissue may contribute to sphincteric action. Woodburne (1960) raised this point and Pennington and Lund (1960) described a loop of elastic tissue in the submucosa of the posterior urethra. The loop is in the form of a horseshoe, the junction of the limbs lying in the anterior wall of the membranous urethra with the limbs embracing the urethra, running upwards and backwards and ending behind the urethral crest and verumontanum. This finding was confirmed in this series. Clearly the effect of this elastic loop would be to shorten and close the mucosal tube round which it lies.

Yet another factor besides muscular and elastic contraction has been suggested as being necessary for complete continence. Millin (1969) put foward the view that muscular contraction alone could reduce the lumen to a very small diameter but could not completely close it. The final seal was provided by the mucous membrane acting as a plug or choke when squeezed by the surrounding sphincter. Zinner *et al.* (1976) have restated and elaborated this hypothesis. They write: "To maintain total continence the urethral lumen must seal completely. The type of seal requires three major elements: inner softness, inner compression and outer tension." Millin visualised the urethral plug as consisting of longitudinal folds of mucous membrane thrown into relief as the lumen narrowed. The findings in the present series suggest that in the male the mucosal factor in continence may take a special form. The shape of the cross section of the posterior urethra when closed is an inverted U (*i.e.* convex anteriorly). This is due to the forward projection of the urethral crest. As Figures 13 and 14 show, the crest is a substantial structure with a central keel of muscle and it is surrounded by the smooth muscle sphincter. When the sphincter contracts the urethral crest would be forced into the lumen, so producing the effect of a plug, a plug shaped to fit the crescentic lumen of the urethra here.

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The Non-hormone Chemotherapy of Prostatic Cancer

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Summary—Seventeen patients with hormone resistant prostatic cancer were treated with chemotherapeutic drugs. An overall response rate of 64% was obtained.

In this study the toxicity rate was 29%. The problems of defining response in prostatic cancer are discussed and a protocol for the future is outlined.

The observation that metastatic carcinoma of the prostate responded to androgen suppression has been the mainstay of treatment of this disease for almost 40 years (Huggins and Hodges, 1941). However, about 30% of patients who receive hormone therapy can be expected to become refractory to treatment and to die of their disease within 48 months of the commencement of therapy (Byar, 1973). Other forms of hormone treatment (*e.g.* hypophysectomy), whilst resulting in symptomatic relief from bone pain, have little effect on the overall survival of the patient. This problem of "hormone escape" has resulted in a variety of trials of chemotherapeutic agents to combat this disease.

An analysis by the National Cancer Institute of the effectiveness of single agents against prostatic cancer has been discouraging (Wasserman *et al.*, 1975). However, preliminary reports on several drugs, both singly and in combination, have been sufficiently encouraging to promote further controlled studies to evaluate their effectiveness (De Wys, 1975; Scott *et al.*, 1975; Tejada and Cohen, 1975; Merrin *et al.*, 1976). Two agents in particular, cyclophosphamide and 5-fluorouracil, have been claimed to have been associated with encouraging objective responses. Newer agents such as Adriamycin, CCNU, DTIC and procarbazine are currently being assessed by trials in progress (Murphy *et al.*, 1976; De Wys *et al.*, 1977; Johnson *et al.*, 1977; Tejada *et al.*, 1977).

This paper reports the experience of chemotherapeutic agents employed against prostatic cancer at the Royal Marsden Hospital between 1973 and 1976.

Patients and Methods

The following criteria were required for entry into the study:

1. Histologically proven prostatic cancer.
2. No change in hormone therapy within 3 months prior to treatment.
3. No other known malignant disease.
4. Patients expected to survive more than 90 days.
5. Non-hormone chemotherapy had not been previously given.
6. An objective, measurable criterion available to assess response.

Seventeen patients were treated in this study. Sixteen had skeletal metastases and one had pulmonary metastases only. With one exception, all had been referred following the failure of either previous hormone therapy or local radiotherapy to control their disease. One patient received non-hormone chemotherapy as his initial treatment. He had refused orchiectomy and was considered unsuitable for oestrogen therapy on account of severe cardiovascular disease. His response to treatment is discussed later (see Results). Of the 17 patients, 4 had received oestrogen therapy alone, one had undergone orchiectomy alone, one had received radiotherapy alone and 10 had received more than one of the above in their previous management.

Patients studied received one of 3 regimes; all regimes were repeated every 2 weeks as in-patients:

(*a*) Methotrexate 100 mg intravenously.
(*b*) Methotrexate 100 mg + cyclophosphamide 500 mg intravenously.
(*c*) Methotrexate 100 mg + cyclophosphamide 500 mg + 5-fluorouracil 500 mg intravenously.

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Table 1 Overall Response to Chemotherapy

Drug(s)	*No. of patients*	*Objective response*	*Subjective response*	*Progression no response*	*Side effects*
Methotrexate	11	2 (18%)	5 (45%)	5 (45%)	3 (27%)
Methotrexate/cyclophosphamide	4	3 (75%)	3 (75%)	1 (25%)	0 (0%)
Methotrexate/cyclophosphamide/ 5-fluorouracil	2	1 (50%)	2 (100%)	0 (0%)	2 (100%)
Total	17	6 (35%)	10 (58%)	6 (35%)	5 (29%)
Total overall response = 11/17 (64%)					

Patients who were judged to have responded to treatment, or remained static, continued on their regime indefinitely or until relapse occurred. Patients were withdrawn from this therapy if relapse occurred.

Criteria for Assessment of Response

Partial objective response:

1. Fifty per cent reduction in measurable, palpable soft tissue tumour if present.
2. Return of elevated serum acid phosphatase to normal.
3. Recalcification of osteolytic lesions on plain radiography.
4. No increase in size of pre-existing lesions or no new lesions appearing.
5. Objective improvement in isotope bone scan appearances.

Subjective response:

1. Improvement in pain.
2. Improvement in appetite.
3. Weight gain.
4. Return of voluntary micturition in cases of urinary retention not treated by transurethral resection.

Cystoscopy and bimanual examination, serum acid phosphatase estimation, skeletal survey and isotope bone scan were performed on all patients at an initial in-patient assessment. Cystoscopy and bimanual examination, acid phosphatase estimation and skeletal survey were repeated at 3 months, and isotope bone scanning at 6 months after commencing therapy. Patients were specifically questioned about drug side effects after each course of treatment.

Results

Tables 1, 2 and 3 show the pattern of response to the 3 regimes. With Methotrexate alone, 2 patients showed a partial objective response. In the first case, a large prostatic mass was estimated to have decreased in size by 50% on bimanual examination. The gland, which had initially been hard, was also noted to have become soft. The second patient had previously received radiotherapy alone to his prostate. He presented with pulmonary metastases and also had a history of ischaemic heart disease. He refused orchiectomy and was considered unsuitable for oestrogen therapy. After 7 courses of Methotrexate his pulmonary metastases had remained static and he was in good general health.

The main subjective response was in respect of pain. This was assessed in the absence of significant analgesia. Two patients who had not undergone transurethral resection experienced return of voluntary micturition following urinary retention.

Two of the 4 patients who received Methotrexate and cyclophosphamide showed a marked reduction in the size of pelvic masses. One of these patients had received no prior therapy for reasons

Table 2 Objective Response to Chemotherapy

Drug(s)	*Reduction in size of mass*	*Radiological response*	*Bone scan response*
Methotrexate	1	1	0
Methotrexate/cyclophosphamide	2	0	1
Methotrexate/cyclophosphamide/ 5-fluorouracil	1	0	0

Table 3 Subjective Response to Chemotherapy

Drug(s)	*Pain*	*Urinary symptoms*
Methotrexate	4	2
Methotrexate/cyclophosphamide	3	—
Methotrexate/cyclophosphamide/ 5-fluorouracil	2	—

previously explained. The bone scan of a third patient had reverted to normal 6 months after the initial scan. The latter had shown multiple "hot spots" consistent with metastatic disease. This response could not be correlated with a biochemical measurement since his plasma acid and alkaline phosphatase levels were normal throughout his treatment. All of the subjective responses were in respect of bone pain.

Two patients were treated with Methotrexate, cyclophosphamide and 5-fluorouracil; one had a large pelvic mass which was reduced to 30% of its original size after 12 weeks of treatment. Both patients experienced relief of pain due to bony metastases.

No patient in any treatment group showed a return to normal of an elevated acid phosphatase value. Eight patients had elevated levels prior to treatment and 3 of these responded to therapy in respect of bone pain. The acid phosphatase values fell slightly on treatment but did not return to normal.

The time relationship between responses and the duration of treatment is illustrated in the Figure. Only positive responders are shown. In each case, treatment was continued until relapse occurred. Responses were assessed after each course of treatment by full clinical examination and by examination under anaesthesia at 12 weeks.

With one exception, all responses occurred within 10 courses of treatment. The 2 patients who received fewer than 6 courses of treatment died suddenly of unrelated causes. The patient who received Methotrexate alone died of a pulmonary embolism and the patient who received Methotrexate, cyclophosphamide and 5-fluorouracil died of a myocardial infarction. One patient was not considered to have shown a positive response until 22 courses of treatment had been completed. In this case, response was assessed on repeat isotopic bone scan. It is impossible to know at what point response really occurred since the timing of re-assessment is governed by the technical factors related to scanning.

The commonest side effects experienced were nausea, vomiting and stomal ulceration. These were controlled with symptomatic treatment and in no case was treatment deferred or curtailed because of side effects. One patient suffered a gastrointestinal haemorrhage after his first dose of Methotrexate, cyclophosphamide and 5-fluorouracil.

Discussion

Clinicians faced with an elderly patient suffering from prostatic cancer which has become refrac-

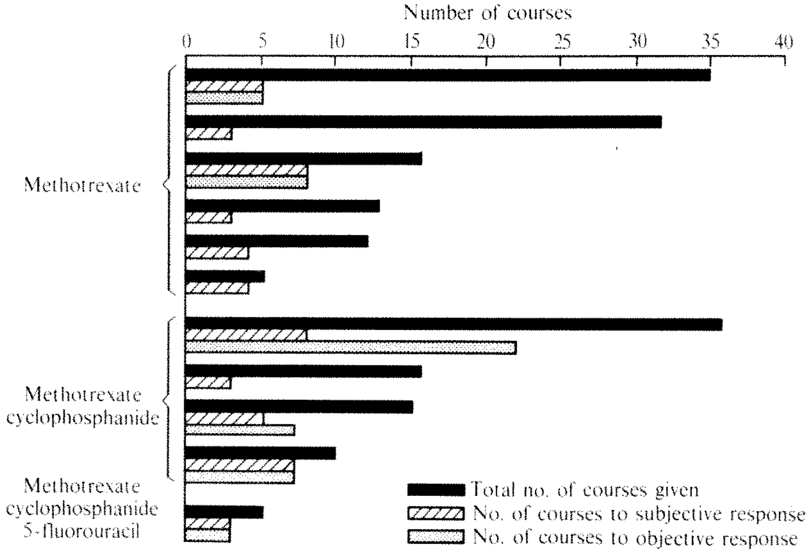

Fig.

tory to hormone treatment face a difficult dilemma. Experience of chemotherapy in this disease is still limited and most chemotherapeutic agents have toxicity and potentially harmful side effects. Whilst agents are still in the stage of evaluation, it is important that they at least do no harm.

This preliminary study reports the experience of chemotherapy in the management of advanced prostatic cancer at the Royal Marsden Hospital over a 3-year period (1973-76). An overall response rate of 64% was obtained. The toxicity rate was low and no patient had to be withdrawn from therapy because of drug side effects. However, the number of patients in the study was small and the regimes were not administered according to a randomised protocol. Therefore no conclusions can be offered concerning the efficacy of one treatment over another.

The difficulty in assessing prostatic cancer lies in defining the point at which response occurs during treatment. In respect of subjective responses, some patients received up to 8 courses of treatment before any response was noted. It is possible that trials designed to cross over to another treatment after 2 or 3 courses may miss a potential response. An objective response is considerably more difficult to assess. The majority of patients do not have a lump which is easily accessible to measurement and reliance on bimanual examination of the prostate or a pelvic mass is well recognised to be unreliable. An accurate assessment of local primary disease may depend on the future availability of the newer techniques of ultrasonic and computerised axial tomographic scanning. Our criteria of response were based on those recommended by the National Cancer Institute. The inclusion of urinary function and the so-called "steady state" of metastases is open to criticism, but in our view this merely reflects the difficulty of defining response in prostatic cancer.

It is our view that the overall results of this study in respect of response and toxicity are encouraging enough for a controlled Phase II study to be undertaken. A combination protocol of cyclophosphamide, 5-fluorouracil and hydroxyurea has been proposed and it is hoped that this will give further guidance in the management of prostatic cancer which is not responsive to conventional hormone therapy.

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Urethral Supersensitivity and Occult Urethral Neuropathy

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Summary—The phenomenon of postural increases in urethral tone in patients with neuropathic bladder dysfunction has been investigated and, using the technique of simulated alterations in posture, a humoral response of urethral smooth muscle has been demonstrated. Serial measurements of circulating catecholamines have shown that a close correlation exists between the contraction of urethral smooth muscle and the variations in circulating catecholamines brought about as part of cardiovascular homeostasis.

Identical urethral responses have been recorded in a group of neurologically intact patients who have urethral outflow obstruction, and it is speculated that these patients may have an occult urethral neuropathy.

It has recently become evident that smooth muscle may be an important component of urethral obstruction in neuropathic bladder dysfunction. The urethral closure pressure in patients with cauda equina spinal lesions is entirely due to smooth muscle activity under alpha-adrenergic influence and in these cases urethral tone increases in response to a change of posture (Abel *et al.*, 1974). In an investigation of neuropathic vesico-urethral dysfunction due to spinal trauma at various levels, Sham Sunder *et al.* (1978) demonstrated that smooth muscle tone contributed to urethral obstruction at all levels of spinal lesion and furthermore that in each patient studied a change of posture produced a greater increase in urethral pressure than the rise in intravesical pressure resulting from transmission of abdominal pressure. This inappropriate postural effect was due to alteration in smooth muscle tone and was dependent upon (*a*) the level of the spinal lesion in respect of the sympathetic efferents to the bladder and urethra and (*b*) the integrity of the sacral cholinergic reflex arcs.

The hypothesis was that changes in urethral smooth muscle activity may be a result of denervation hypersensitivity to variations in circulating catecholamine levels. The postural alteration in plasma catecholamines is due to the involvement of the sympathetic nervous system in cardiovascular homeostasis. On assuming the upright position there is a decrease in venous return to the heart due to pooling of blood in capacitance vessels in the lower extremities. The resulting reduction in cardiac stroke volume causes a drop in blood pressure, which triggers the carotid sinus feedback reflexes. This in turn increases tonic adrenergic discharges to arterioles to maintain arterial pressure. The major proportion of circulating noradrenaline is derived from adrenergic neuronal discharge releasing the neurotransmitter into the circulation. Circulating adrenaline levels similarly alter in response to postural change as a result of increased adrenal medullary secretion produced by diffuse adrenergic discharge.

Since posturally mediated increases in urethral tone occur in neuropathic bladder dysfunction, measurements of the urethral pressure profile with patients both supine and sitting up has been added to our routine urodynamic investigation. Whilst the urethral closure pressure in normal individuals does not usually increase on sitting, from this investigation a group of neurologically normal patients has been identified in whom an inappropriate postural increase in urethral tone occurred. These cases all had urethral outflow obstruction, defined by standard pressure-flow videocystourethrography.

The present study tests the hypothesis that urethral smooth muscle supersensitivity is the mechanism responsible for posturally mediated

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alterations in urethral tone, seen in patients with neuropathic vesicourethral dysfunction but also occurring in patients with no identifiable neuropathy. The similarity of the urethral responses in this latter group suggests that these patients may have an occult urethral neuropathy.

Patients and Methods

In order to elucidate factors causing a postural increase in urethral tone, a method which simulates a change of posture was used. Simulated postural change was produced by the inflation of pneumatic cuffs applied to both thighs (Fig. 1). When inflated, the cuffs produce a reduction in right heart venous return similar to that resulting from a change of posture from flat to sitting. Changes in spinal reflex activity in either striated or smooth muscle, resulting from increased afferent stimuli from the pelvic viscera or pelvic floor, were thus excluded. Increase in the urethral pressure under these conditions could therefore be attributed to a humoral mechanism.

During each stage of the investigation, circulating catecholamine levels were measured to identify any correlation with urethral pressure alterations.

The investigation of posture influence on the urethral pressure profile was divided into 3 parts:

1. Six male patients with various types of neuropathic bladder dysfunction were studied and postural and "cuff" responses demonstrated. In 4 of these cases simultaneous catecholamine levels were measured. The cause of the neuropathic bladder dysfunction in each patient is shown in Table 1.

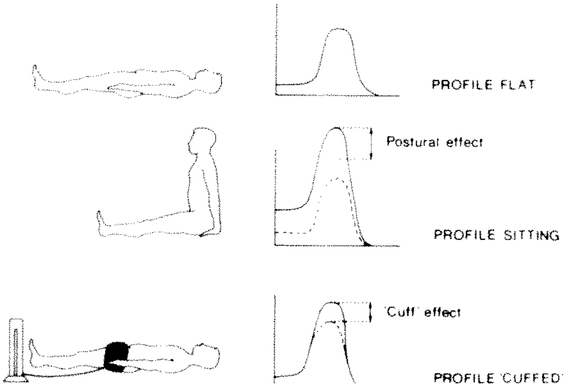

Fig. 1 Simulated postural change with pneumatic cuffs in neuropathic vesicourethral dysfunction.

Table 1 Neurological Lesions in Patients with Neuropathic Vesicourethral Dysfunction

Patients	*Neurological lesion*
R.J.	Incomplete paraplegia. Fracture dislocation L1 on L2.
F.M.	Post-traumatic hemiparesis.
A.C.	Incomplete spastic tetraplegia. Fracture dislocation C6 on C7.
J.K.	Complete T6 traumatic paraplegia.
J.C.	Peripheral bladder denervation following abdominoperineal excision of the rectum.
R.M.	Peripheral bladder denervation following abdominoperineal excision of the rectum.

2. Five patients, 4 female and one male, with urethral obstruction as defined by low urinary flow rates despite normal or elevated detrusor voiding pressures and normal bladder neck opening seen on synchronous radiographic screening, were investigated in similar fashion, assessing postural changes in urethral tone and simulated postural responses. None of these patients had any known neurological defect.
3. Three patients from this latter group, who showed marked postural and "cuff" responses, had serial catecholamine levels measured at each stage of the urethral pressure profile investigation.

Urethral Pressure Profiles

Urethral pressure profiles were measured using the technique previously reported (Sham Sunder *et al.*, 1978). Profiles were written on an X-Y plotter to facilitate superimposition for comparative purposes. In all cases profiles were recorded with the bladder empty, and some with the bladder both empty and full. In those patients where catecholamine levels were determined, blood samples were taken using an indwelling venous catheter with remote sampling facility so that, as far as possible, the patient was not aware when each sample was taken. In one case (Fig. 5) an indwelling arterial line was used and continuous arterial pressure monitored.

Catecholamine Assay

Serum adrenaline and noradrenaline levels were measured by the technique described by Turton and Deegan (1973). The assay was based on the extraction technique of Vendsalu (1960) and the fluorescent conditions of Haggendal (1963). The normal values for catecholamines, previously reported by Turton and Deegan (1973) are shown in Table 4.

Investigative Procedure

1. Under resting conditions, with the patient supine and the bladder empty, a blood sample for the basal catecholamine level was taken, followed immediately by recording of the first urethral pressure profile.
2. The patient was then moved to the seated position. An interval of approximately 4 min was allowed between each manoeuvre in the investigation for equilibration of both the urethral pressure and the serum catecholamine level; thus 4 min after assuming the sitting position a further catecholamine sample was taken and the profile recorded.
3. The patient was put flat once more and another blood sample taken and urethral pressure profile recorded.
4. The pneumatic cuff on each thigh was then inflated to 20 mmHg above the diastolic blood pressure and under these conditions a further blood sample was taken and the profile recorded.
5. Finally, a single dose of 10 mg intravenous phentolamine (Rogitine, Ciba) was given and the last blood sample withdrawn and profile recorded.

Results

(Definitions of the urethral pressure profile measurements in this study conform to the standards proposed by the International Continence Society.)

Postural and Cuff Responses in Neuropathic Bladder Dysfunction

A typical urethral pressure profile recorded in a patient with a peripherally denervated bladder following abdominoperineal excision of the rectum is shown in Figures 2 A and B. In the supine position there is no midurethral peak (Fig. 2 A, F) and the alteration of the configuration of the profile with the increase of the maximum urethral pressure resulting from a change of posture is clearly seen (Fig. 2 A, S). The effect of inflation of pneumatic thigh cuffs producing a peak of pressure in the supine position is shown (Fig. 2 B, C), and the subsequent effect of alpha-adrenergic blockade returning the profile to its former configuration is demonstrated (Fig. 2 B, P).

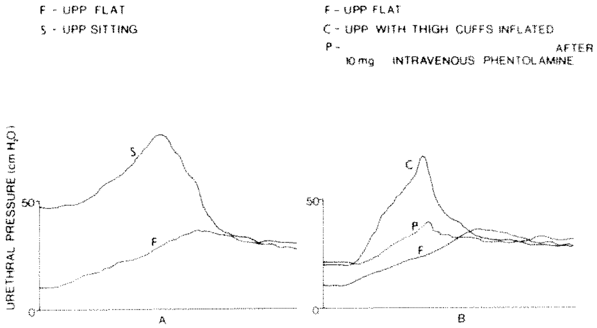

Fig. 2 The effect of posture A, pneumatic cuffs B, and Phentolamine B:P on the urethral pressure profile of a patient with vesicourethral dysfunction following abdominoperineal excision of the rectum.

Similarly, Figure 3 shows postural (Fig. 3 A, S) and cuff (Fig. 3 B, C) responses recorded in a patient (J.K.) with supranuclear neuropathic bladder dysfunction following spinal trauma.

From these diagrams it can be seen that the increase in the urethral closure pressure produced by a change of posture may be defined as the "postural effect". On the assumption that intra-abdominal pressure is normally transmitted equally to the bladder and urethra, the postural increase in closure pressure is inappropriate. The "cuff effect" is the increase in the maximum urethral pressure induced by inflation of the pneumatic cuffs, as in this circumstance the bladder pressure remains constant.

The values of postural and cuff responses (cm H_2O) in each of the patients with neuropathic bladder dysfunction are shown in Table 2.

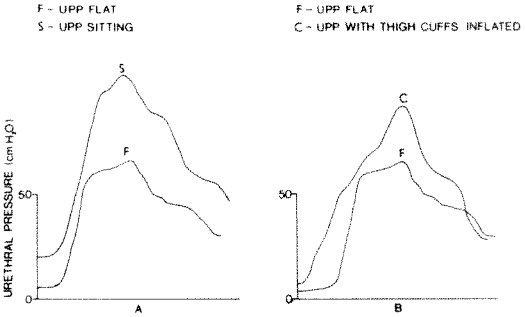

Fig. 3 The effect of posture A and pneumatic cuffs B on the urethral pressure profile of a patient with supranuclear bladder dysfunction.

Table 2 Maximum Urethral Pressures, Postural, Cuff and Phentolamine Effects in Patients with Neuropathic Vesicourethral Dysfunction

	Maximum urethral pressure (cm H_2O)				*Bladder pressure (cm H_2O)*		*Postural effect**	*Cuff effect†*
	Flat	*Sitting*	*Cuffed*	*After phento. cuffed*	*Flat*	*Sitting*		
R.J.	64	116	87	47	10	19	43	23
J.K.	65	107	92	-	13	36	19	27
A.C.	108	132	110	36	8	17	15	2
F.M.	38	56	54	23	0	8	10	16
J.C.	37	81	71	40	10	48	6	34
R.M.	88	125	114	80	14	34	17	26

* (*i.e.* increase in urethral closure pressure on sitting).
† (*i.e.* increase in urethral closure pressure when cuffed).

Catecholamine Values in 4 Patients with Neuropathic Bladder Dysfunction

The serial catecholamines were measured at each stage of the investigation of 4 patients with neuropathic bladder dysfunction. The postural and cuff responses are expressed as percentage increases of the resting urethral closure pressure (Fig. 4).

Postural and Cuff Responses in Neurologically Normal Patients with Outflow Obstruction

The urethral pressure profiles of a female patient with urethral obstruction, showing an inappropriate postural response and a "cuff" response, are shown in Figures 5 A, B and C. In this patient a continuous recording of arterial blood pressure was made and is shown in the bottom half of the figure. The effect of alpha-adrenergic blockade on both the urethral pressure profile whilst cuffed, and the arterial blood pressure, is shown in Figure 5 C.

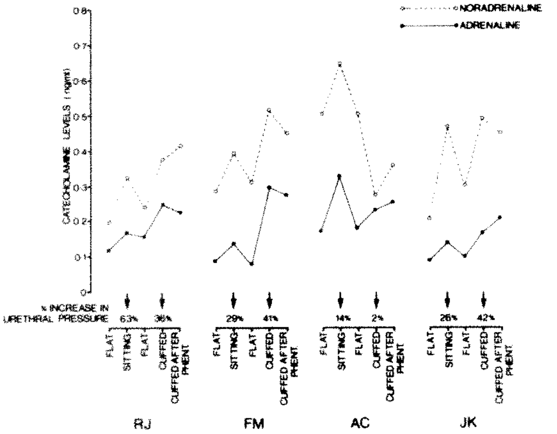

Fig. 4 Catecholamine levels in patients with neuropathic vesicourethral dysfunction.

Table 3 shows postural and cuff responses in each of the 5 patients with urodynamically demonstrated urethral obstruction and no definable neuropathy.

Catecholamine Values in Neurologically Normal Patients with Urethral Obstruction

The catecholamine values corresponding to each step in the investigation were measured in 3 patients with urethral obstruction; postural and cuff responses were expressed as percentages of the resting urethral closure pressure (Fig. 6).

Discussion

The purpose of this study was to confirm that changes in urethral tone consequent on a change of posture are due to a decentralisation supersensitivity phenomenon of urethral smooth muscle, which responds to alterations in circulating catecholamine levels brought about as part of cardiovascular homeostasis.

It was necessary, therefore, to measure postural urethral responses together with changes in circulating catecholamines, then to simulate a change of posture to see whether catecholamine levels alter under these conditions and whether an increase in the urethral pressure profile was produced. The use of simulated postural change excluded alterations in spinal reflex activity of either striated or smooth muscle, as no afferent impulses are stimulated if the position of the patient remains unchanged.

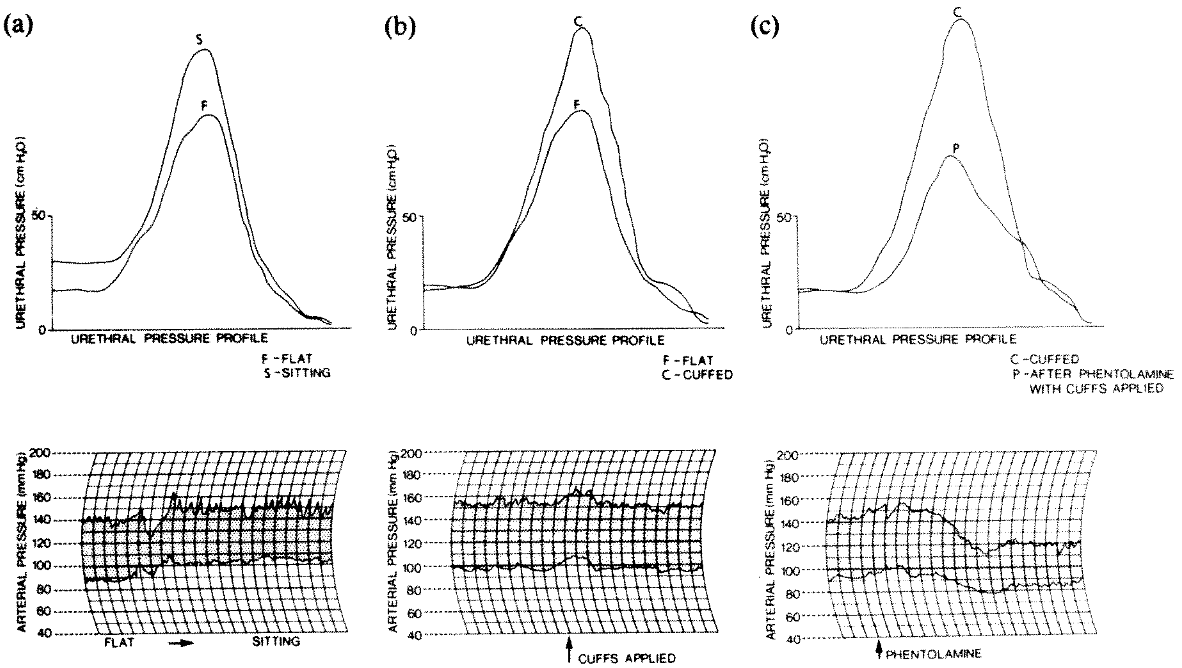

Fig. 5 (a) Urethral pressure profile and arterial pressure response to postural change in a neurologically normal female patient with outflow obstruction. (b) Effect of pneumatic thigh cuffs on the urethral pressure profile and arterial pressure of a female patient with outflow obstruction. (c) The effect of phentolamine on the urethral pressure profile and arterial pressure in a female patient with outflow obstruction with pneumatic thigh cuffs applied.

From the results of serial catecholamine estimations it was seen that the pneumatic thigh cuff inflation provoked increases of both adrenaline and noradrenaline levels similar to those produced by sitting up. As an increase in the urethral pressure was also produced by inflation of the thigh cuffs, this is corroborative evidence that the urethra was responding to this humoral mechanism. It is of interest that the patient with neuropathic bladder dysfunction (A.C.), in whom a postural response was not reproduced by pneumatic cuffs, showed no significant increase in catecholamines on inflation of the cuffs. The neurological damage in this case had caused severe muscular wastage so that the venous capacity in the legs was considerably reduced and cuff inflation was ineffectual.

Continuous recording of arterial blood pressure taken in a neurologically normal patient suggests that changes in catecholamine levels are part of a cardiovascular homeostatic mechanism, for at each stage of the investigation arterial blood pressure was constant. (The slight increase in arterial pressure in the sitting position is explained

Table 3 Maximum Urethral Pressures, Postural, Cuff and Phentolamine Effects in Neurologically Normal Patients with Outflow Obstruction

	Maximum urethral pressure (cm H_2O)				*Bladder pressure (cm H_2O)*		*Postural effect (cm H_2O)*	*Cuff effect (cm H_2O)*
	Flat	*Sitting*	*Cuffed*	*After phento. cuffed*	*Flat*	*Sitting*		
J.G.	73	92	90	61	0	8	11	17
L.C.	39	82	55	34	19	29	33	16
M.W.	82	106	116	63	14	24	14	34
S.N.	66	162	84	—	8	16	88	18
H.H.*	62	147	83	24	14	42	57	21

* Male patient with persistent post-prostatectomy obstruction in the region of the membranous urethra.

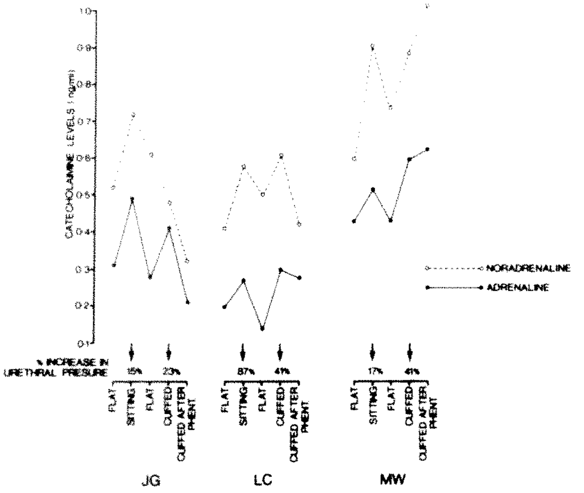

Fig. 6 Catecholamine levels in neurologically normal patients.

by hydrostatic pressure above the level of the transducer when seated.)

The effect of alpha-adrenergic blockade upon the urethral pressure profile recorded under simulated postural conditions indicates that smooth muscle is largely responsible for the increased profile amplitude, as in each case tested the postural and cuff effects were abolished by phentolamine. The hypotension produced by alpha-blockade (Fig. 5 C) might be expected to cause a further rise in circulating catecholamines by stimulation of baroreceptor reflexes. However, this was not a consistent finding, but when present the urethra was unresponsive to this further catecholamine rise, also suggesting that alpha-adrenergic blockade prevents the humorally mediated increase in urethral tone.

The contraction of urethral smooth muscle in response to alterations in circulating catecholamines would therefore seem to be a manifestation of the phenomenon of denervation supersensitivity. This phenomenon was originally described by Elliot (1905) who observed paradoxical dilatation of the denervated iris, and concluded that this was a humoral response. Cannon and Rosenblueth (1949) formulated a "law of denervation" which states that "denervated structures develop a supersensitivity to chemical agents". Use of this phenomenon has been made in the diagnosis of peripheral bladder denervation, where the excessive increase in bladder pressure in response to exogenous cholinergic stimulation forms the basis of a diagnostic test (Lapides *et al.*, 1962; Glahn, 1970). Studies by Trendelenburg *et al.* (1962) and Trendelenburg (1963a and b) have shown that there are 2 components of the denervation supersensitivity phenomenon, dependent upon whether the interruption of the nerve supply is at a pre-ganglionic or post-ganglionic level. The component pertinent to the bladder and urethra is a "decentralisation supersensitivity" as the ganglia are intramural (El Badawi and Schenk, 1974) and the denervation therefore pre-ganglionic. Decentralisation supersensitivity is the less specific of the 2 components and may take up to 2 weeks to develop following denervation, and would adequately explain the inappropriate postural and the cuff responses of the urethra.

Table 4 Normal Resting Catecholamine Values (Mean ± SD)

ADRENALINE	0.15 ± 0.08 ng/ml (n = 20)
NORADRENALINE	0.30 ± 0.13 ng/ml (n = 20)

Replicate analysis of standard solutions of adrenaline and noradrenaline gives results of:

± 0.01 for ADRENALINE and
± 0.02 for NORADRENALINE (n = 20)

Thoenen (1972) describes a teleological explanation for supersensitivity and states that the phenomenon "can be considered to be a compensatory mechanism which helps to maintain homeostasis of autonomic functions after destruction of a greater part of the sympathetic nervous system. The denervated organs no longer receive nerve impulses which normally control their activity, but may still take part in some general reaction of the organism by their increased reactivity to circulating catecholamines". This aspect of the mechanism could equally well be applicable to urethral function as to that of any other organ.

The observation of a similar phenomenon in patients with urethral obstruction but without a demonstrable neurological lesion provokes the interesting speculation that these patients may have a hitherto undetected selective urethral neuropathy. The male patient in whom these urethral responses were demonstrated had previously had a prostatectomy and perhaps the urethral nerve supply was damaged as a result of pressure atrophy from progressive prostatic enlargement. In the female patients, however, an occult urethral neuropathy may be responsible, and the existence of urethral smooth muscle supersensitivity would provide a rational explanation for the condition of outflow obstruction in the female when no urethral narrowing can be demonstrated by calibration. Furthermore, the supersensitivity phenomenon would explain both the variations in symptomatology and the inconsistent urodynamic findings in these patients since the degree of obstruction would alter depending upon variations in catecholamines in circulation.

It is concluded that in neuropathic vesicourethral dysfunction, decentralised smooth muscle may contract and therefore contribute to outflow obstruction because it is supersensitive to circulating catecholamines.

A similar mechanism is also seen in some neurologically normal patients who display an identical phenomenon and therefore may have an occult urethral neuropathy which would explain the apparent outflow tract obstruction in these cases.

Acknowledgements

The authors wish to thank Mr N. O. K. Gibbon for allowing his patients to be included in this investigation and for helpful advice and criticism in the preparation of this paper, Mr K. R. Krishnan and Mr R. M. Jameson for allowing their patients to be included in this study and Mr K. Biggs, Medical Faculty Artist, University of Liverpool, for preparing the illustrations.

Part of this work is included in a thesis to be presented by K. F. Parsons to the University of Liverpool for the degree of ChM.

Addendum

Whilst in 4 cases of neurologically normal females with urethral outflow obstruction included in this study there was no obvious case for a "urethral neuropathy", a group of patients has come to light who appear to develop this condition as judged by urethral postural and cuff responses.

Recent studies have shown that patients who have had a hysterectomy, either by the abdominal or vaginal route, may demonstrate these abnormal urethral responses postoperatively, suggesting that interruption of the nerve supply to the urethra may be implicated in persistent urinary symptoms in these patients. A full investigation of this phenomenon is currently in progress and will be documented in detail.

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Detection of Urethral Incompetence in Women using the Fluid-Bridge Test

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Summary—A new test for detecting urethral incompetence during coughing has been used in the investigation of women with urinary incontinence. The test detects fluid descending into the urethra and the result is positive if a "fluid-bridge" is established between the bladder and a test point in the urethra. For the purpose of this study the test point selected was 0.5 cm from the urethrovesical junction.

Sixty-seven incontinent patients and 23 women with normal urinary control were studied. Thirty-nine of the 67 incontinent women had a positive fluid-bridge test compared with only one of the women in the control group. The difference between the test results in the 2 groups was highly significant ($P<0.001$).

In the incontinent patients a diagnosis was made after cystometry had been performed and after the urethral closure pressure profile had been measured. In 46 (69%) of these 67 patients there was agreement between the diagnosis made following these urodynamic investigations and the one made from the new test.

The advantages and shortcomings of the new method are compared with those of other stress tests in current use.

Stress urinary incontinence in women may be demonstrated during clinical examination. However, it is not always possible to do this, even when the patient is standing up. Actual leakage may become evident on radiological screening of the urethra, but not necessarily. During stress the distal closure mechanism may prevent the escape of urine (Farrar *et al.*, 1975) and unless a small momentary beaking of fluid into the proximal urethra is seen during the examination (Ardran *et al.*, 1956), proximal urethral incompetence will not be detected.

A new method of directly detecting fluid entry into the proximal urethra without X-rays has recently been described (Brown and Sutherst, 1978, 1979). Our initial results using this method in clinical practice are presented in this paper. The test is compared with some other methods of clinical and urodynamic investigation.

Patients and Method

Sixty-seven consecutive female patients complaining of stress urinary incontinence were included in the study (mean age 52 years; mean parity 3.2). Twenty-three women with no urinary symptoms were also tested (mean age 33 years; mean parity 0.6). These were women attending for suction curettage as part of investigations for dysfunctional uterine haemorrhage or infertility.

On our unit urodynamic testing includes supine medium-fill cystometry*, provocative tests of detrusor stability (Bates *et al.*, 1970), and measurement of the urethral closure pressure profile (UCPP) using the water infusion method of Brown and Wickham (1969). For the UCPP measurement the bladder volume is standardised at 150 ml, and a double-lumen catheter† is used to allow simultaneous recording of bladder and urethral pressures (Glen and Rowan, 1973). A diagnosis of genuine stress incontinence is made if there is evidence of stress leakage in the absence of detrusor contractions, or if the UCPP measurements are small.

After measurement of the UCPP the catheter

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* In this paper all methods, definitions and units conform to the standards proposed by the International Continence Society (1976, 1977) except where specifically noted.

† Bladder/urethral catheter; Portex Limited, Hythe, Kent, England.

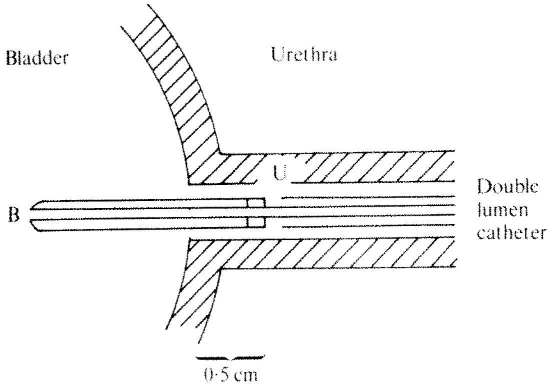

Fig. 1 Diagram showing the position of the double-lumen catheter in the urethra. B: point at which bladder pressure is measured; U: point at which urethral pressure is measured.

is positioned with the side holes at the test point in the urethra. The point selected for this study was 0.5 cm from the urethrovesical junction (Fig. 1). This distance can be judged by reference to the UCPP tracing. The patients are supine for this test and for measurement of the UCPP.

Infusion through the side holes of the catheter is then stopped. The patient is asked to cough and the tracings of bladder and urethral pressure are displayed either on a pen recorder or on a storage cathode ray tube screen. Figure 2 shows the arrangement of infusion and pressure channels.

If the urethra at the test point remains closed the tracing is similar to that seen in Figure 3a, and we say that the fluid-bridge test is negative; if it opens the tracing is similar to the one in Figure 3b and the test is positive. On some occasions the urethra may be seen to open late in the cough cycle (Fig. 3c).

Results

Thirty-nine of the 67 incontinent women had a positive fluid-bridge test compared with only one of the women in the control group. The difference between the test results in the 2 groups was highly significant ($\chi^2 = 18.0$, $P<0.001$).

In the incontinent patients the results were compared with clinical and urodynamic evidence of genuine stress incontinence. There was agreement between the fluid-bridge test and our eventual diagnosis from clinical and other urodynamic tests in 46 (69%) of the 67 women.

Further breakdown of the results is shown in Figure 4. In the study group 39 patients had a positive test. There was demonstrable stress incontinence in 21 of these but not in the other 18. In 11 of these 18 patients our other urodynamic tests were normal.

Of the 28 patients with a negative test, 8 had demonstrable stress incontinence on clinical examination, and in 2 more the urodynamic diagnosis was sphincter weakness. In 18 there was no evidence of sphincter weakness either by conventional testing or by using the new test.

Discussion

From the results in the control group we can say with some confidence that a negative fluid-bridge test is associated with normal urinary control.

In the study group the correlation is less clear but there are important aspects of the results which are immediately useful. When stress incontinence can be demonstrated during clinical examination no further proof of urethral incompetence is required, but if stress incontinence is

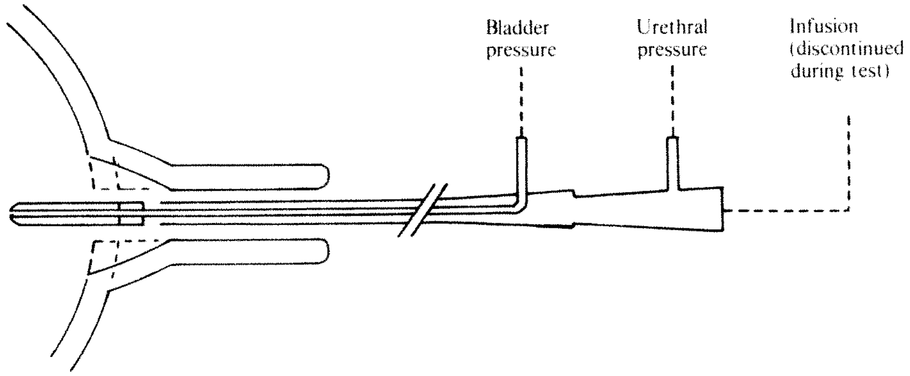

Fig. 2 Diagram showing the arrangement of infusion and pressure lines. During a cough the urethra may open to allow fluid to surround the catheter side holes (as in the diagram).

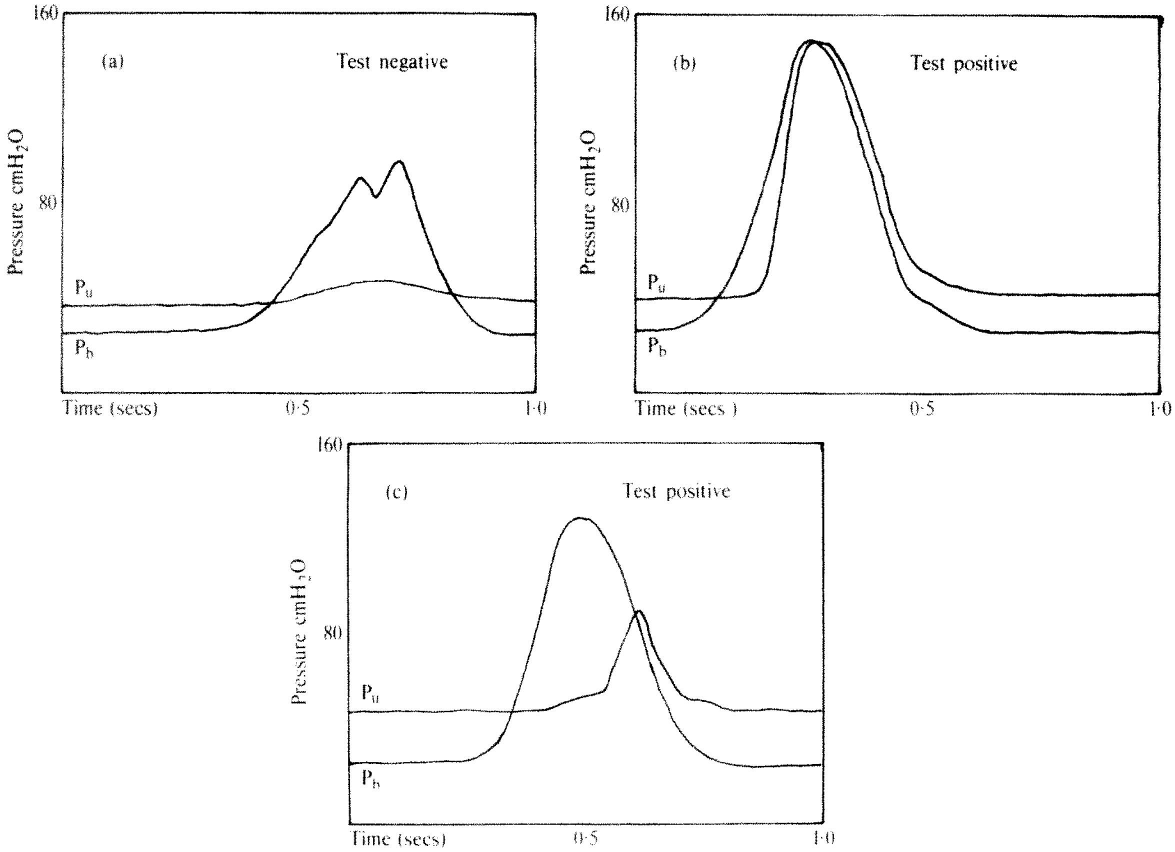

Fig. 3 Pressure tracings of coughs taken from polaroid photographs of CRT screen recordings: (a) the proximal urethra remains closed; (b) the proximal urethra opens to the test point immediately; (c) the urethra opens to the test point late in the cough cycle.

not demonstrable, then no diagnosis can be made without further tests. In this series the fluid-bridge test showed weakness at the bladder neck in 18 (47%) of 38 such patients. Our other urodynamic test identified only 7.

Information gained from the UCPP has proved useful but its measurement is not a dynamic stress test. Methods in which bladder and urethral pressures are measured simultaneously during stress have been devised. They include the use of double pressure balloons (Enhörning, 1961), or double internal microtransducers (Henriksson, 1977). If urethral pressure falls below bladder pressure during stress it is inferred that urine leakage must occur. This interpretation of the results relies on theories of pressure transmission from the abdomen (Green, 1968), but the tests cannot prove that the bladder neck opens during stress. If the urethra opens, transmitted hydrostatic pressure from the bladder will also reach the test point, causing confusion in the interpretation of the urethral pressure recording.

The fluid-infusion method of measuring urethral pressure is not usually suitable for stress testing because the response time of the apparatus is too slow. The bladder channel can respond quickly because of the abundance of fluid around the catheter tip, but the response time of the urethral channel is dependent upon the rate of infusion. If the infusion is discontinued the compliance requirements of the apparatus are not satisfied and during sudden rises of pressure the urethral line cannot respond. Only if the bladder neck opens so that the urethra at the test point becomes wet, does the pressure tracing take on the "cough-incompetent" or "positive" pattern.

Since there was a negative fluid-bridge test in 8 patients with demonstrable stress incontinence it is clear that the test, as we have performed it, does not detect all cases of sphincter weakness.

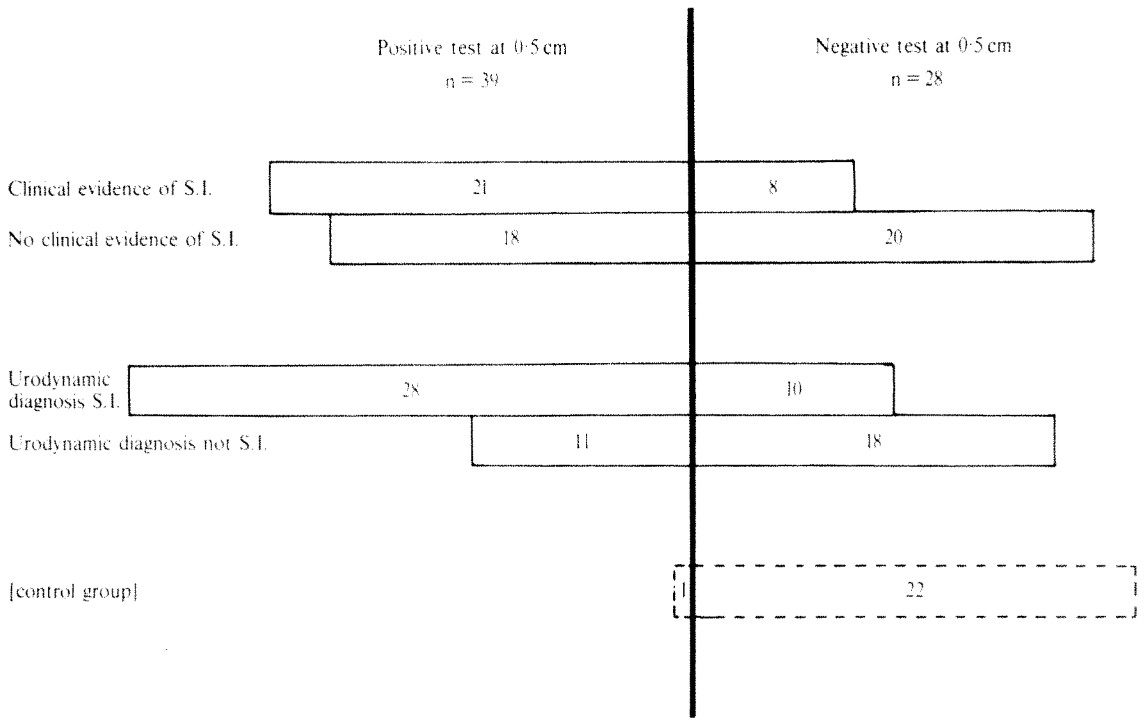

Fig. 4 Results of the fluid-bridge test compared with clinical and urodynamic evidence of stress incontinence. Clinical evidence was an observed leak during coughing; "urodynamic diagnosis" was the final diagnosis, taking into account the results of cystometry and UCPP measurement, but excluding the results of the fluid-bridge test. (S.I. = stress incontinence.)

The reasons for this may include the following. There may be variations in the force of the cough; sometimes women cough very gently and have to be asked to do so more vigorously. The presence of the catheter may occlude the internal urethral meatus; this might be less likely to happen if a catheter of small calibre were used. The position of the patient during the test may be important since stress incontinence is not as common when a woman is lying down as when she is standing up. The choice of a test point 0.5 cm from the urethrovesical junction may be less satisfactory than a point closer to the bladder; in 22 of the control patients it was possible to position the side holes of the catheter 2 to 3 mm from the urethrovesical junction and still register a negative test. Finally, the catheter may move in the urethra during a cough; there is a tendency for it to be forced down the urethra during stress, thereby moving the side holes to a position of greater urethral wall pressure and giving a false negative result.

In some patients the opening of the urethra appears late in the cough cycle. It may be that in these patients there is a different mechanism of leakage. If their incontinence is dependent on descent of the pelvic floor, for example, this might take a longer time to develop than the duration of a short cough. Further studies are needed on this group of patients.

We conclude that the fluid-bridge test is a useful adjunct to standard urodynamic investigation. A positive test is hard to ignore when collating data for the final diagnosis, and it appears to be particularly helpful in identifying urethral incompetence in those patients where stress incontinence is not demonstrable. The method requires some further development, particularly to clarify the reasons for the number of "false negative" results.

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Scaphoid Megalourethra: a Report of 2 Cases

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Summary—Two cases of scaphoid type megalourethra are reported. Both patients had upper urinary tract dilatation and in one of them massive vesicoureteric reflux was demonstrated. The urinary tract in one patient returned to normal after correction of the megalourethra. The second infant, who had vesicoureteric reflux underwent ureteric reimplantation as well as correction of the deformed urethra. A description of the surgical technique and clinical and radiological follow-up is given.

Megalourethra is a rare congenital anomaly characterised by dilatation of the penile urethra. Two types have been described. In the fusiform variety, the corpora cavernosa and the corpus spongiosum are absent; with the scaphoid type only the corpus spongiosum is absent (Dorairajan, 1963; Stephens, 1963). The condition may be associated with anomalies of the upper urinary tract and with the prune belly syndrome (Johnston and Coimbra, 1970; Cremin, 1971; Shiraki, 1973).

This is a report on 2 infants with the scaphoid type of megalourethra. A description of the surgical correction and clinical and radiological follow-up is given and the possibility that this anomaly causes proximal obstruction is discussed.

Case Reports

Case 1

W.G., born to healthy parents after a normal pregnancy and delivery, was noted at birth to have an enlarged, deformed penis. Definitive surgery was undertaken on the first day without pre-operative radiological evaluation. Redundant skin and urethra were excised and urethroplasty was performed over an 8 FG catheter. The splint was removed a week later and the child voided well. On the tenth post-operative day there was an acute bout of urinary infection. Excretory urography (EU) revealed marked dilatation of the ureters. Micturating cystourethrography (MCU) showed massive bilateral vesicoureteric reflux. Bilateral loop cutaneous ureterostomies were performed. At the age of 2 years, when a repeat EU showed a normal upper urinary tract, the ureterostomies were closed and the ureters reimplanted into the bladder. The urogram 6 months after the operation showed a normal right collecting system and a somewhat dilated left upper tract (Fig. 1). The MCU showed good voiding with the urethra somewhat wider than normal (Fig. 2).

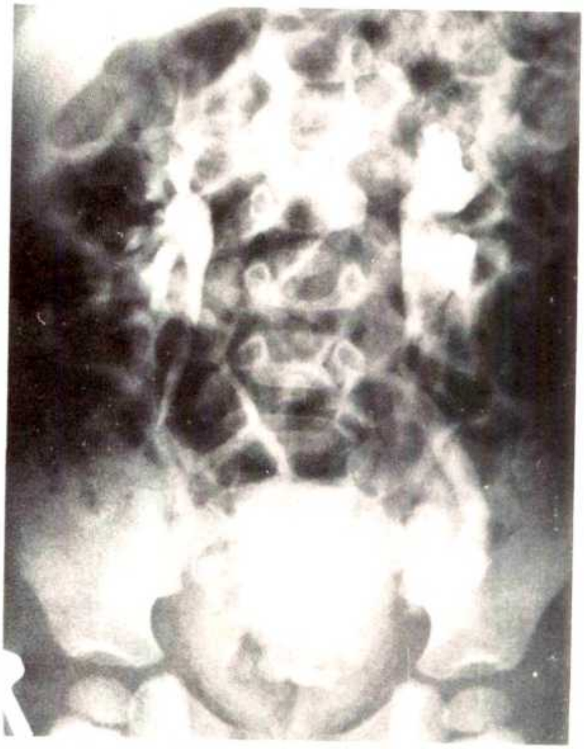

Fig. 1 Case 1. Urogram after closure of ureterostomy, ureteric reimplantation and urethroplasty. Good bilateral excretion. Some dilatation of the left upper collecting system.

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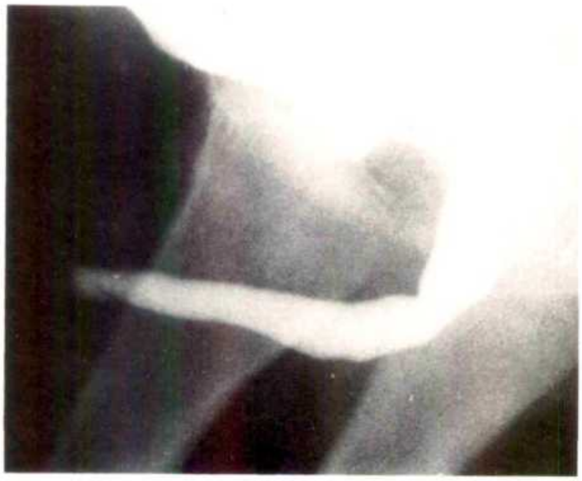

Fig. 2 Case 1. MCU shows a dilated urethra.

Case 2

E.S., born to healthy parents after an uneventful pregnancy and delivery, was found to have an enlarged and deformed penis. The ventral aspect of the penis appeared flail with redundant skin and absent corpus spongiosum. The corpora cavernosa were present. The urethral meatus was normally located (Fig. 3). Physical examination was otherwise negative. The infant voided with a poor stream and a concomitant swelling of the deformed penis was noted. Compression of the urethra caused dribbling from the meatus. EU revealed moderate bilateral upper tract dilatation (Fig. 4). Retrograde urethrography showed a sac-like dilatation of the penile urethra and a normal proximal urethra (Fig. 5). At the age of 1 week the infant underwent urethroplasty. Through a longitudinal incision, redundant skin and urethra were excised and the urethra reconstructed over a 10 FG catheter using interrupted chromic catgut sutures. Circumcision was also performed. On the tenth post-operative day the splint was removed. Two years later the penis was found to have a normal appearance with undeformed erection. EU (Fig. 6) and MCU (Fig. 7) were normal except for a diverticulum of the bladder and some irregularity of the penile urethra.

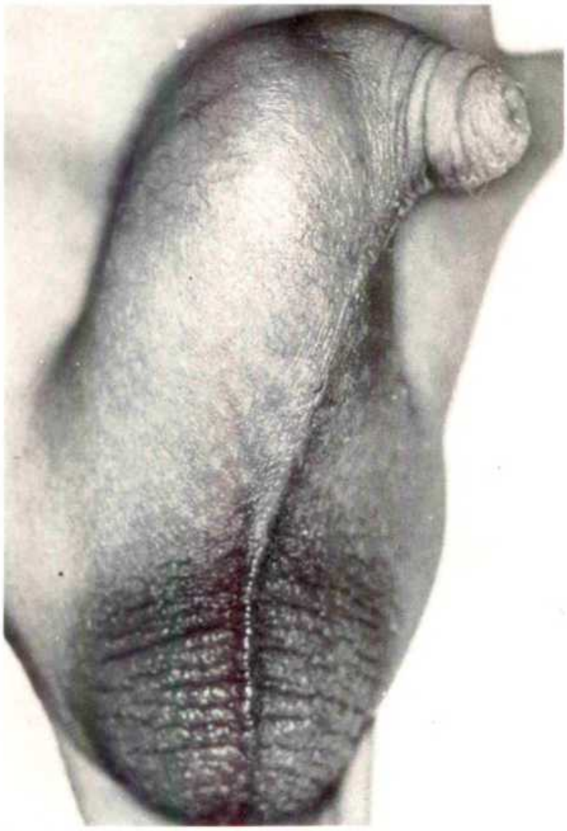

Fig. 3 Case 2. Enlarged deformed penis.

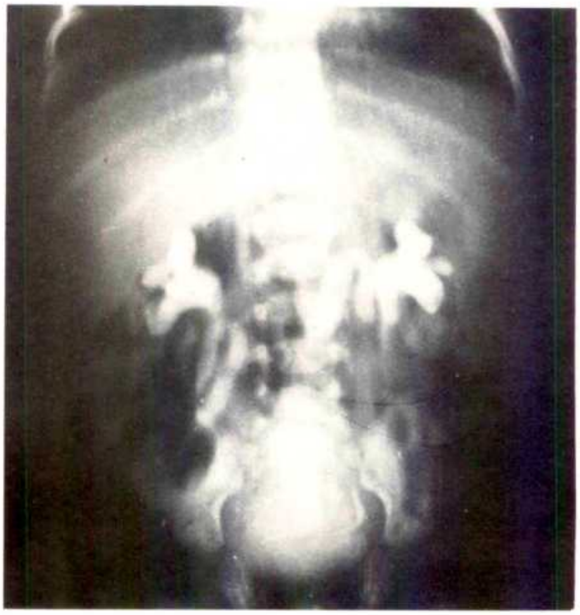

Fig. 4 Case 2. Urogram before operation shows dilated upper collecting systems and tortuous ureters.

Discussion

Megalourethra is a very rare anomaly. So far only 16 cases have been reported in the English literature (Kirchner and Burko, 1975; Slutzki *et al.*, 1977). The fusiform type seems to be the more serious one. Kirchner and Burko (1975) noted that 4 of 5 infants with a fusiform type of megalourethra had associated genitourinary anomalies, while the fifth was stillborn and had a

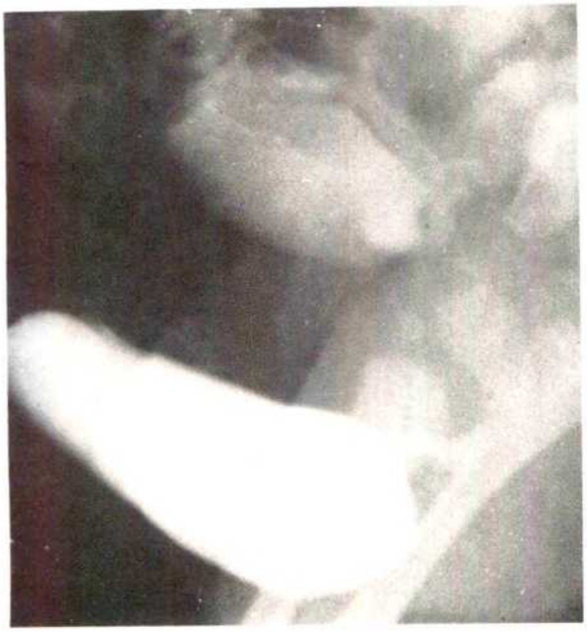

Fig. 5 Case 2. MCU—marked saccular dilatation of the penile urethra.

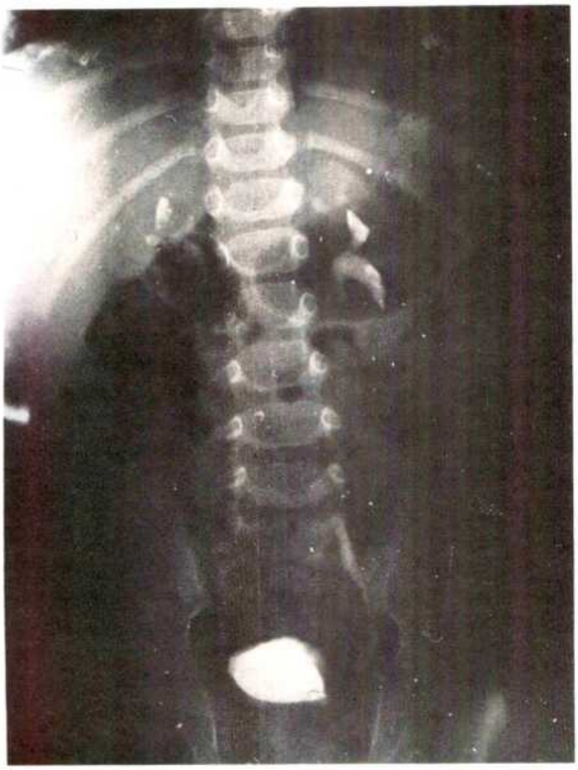

Fig. 6 Case 2. Urogram—post-operative at the age of 2 years: normal upper collecting systems.

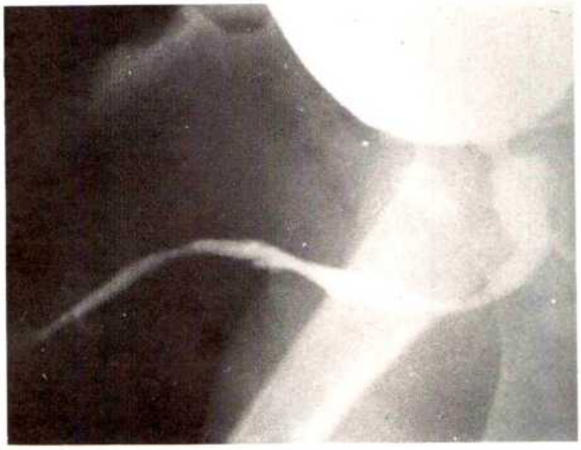

Fig. 7 Case 2. MCU at age 2 years: the urethra has a normal calibre. Slight irregularity of the penile urethra.

rectovesical fistula. One of the 5 is alive. In contrast, 6 of the 9 infants with a scaphoid type of megalourethra had associated anomalies of the upper urinary tract, consisting mainly of ureteric dilatation; 2 of these cases had vesicoureteric reflux (Dorairajan, 1963).

Cystourethrography is difficult to perform, as the catheter coils in the dilated part of the urethra. In our second patient, retrograde urethrography clearly demonstrated the dilated anterior urethra. The appearance is very similar to that of a urethral diverticulum but the communication between the urethral lumen and such a diverticulum is never so large. The post-operative study showed an almost normal urethra. In our first patient, in whom MCU was performed after surgical correction of the anomaly, gross vesicoureteric reflux was demonstrated. This had probably been present prior to the operation as well.

The 2 patients reported here showed marked dilatation of the upper urinary tract on the urogram. As there were no signs of the prune belly syndrome or of urethral obstruction it may be assumed that the sac-like dilatation of the distal urethra caused proximal obstruction with resultant dilatation of the upper urinary tract. This assumption is supported in the second case, where the urinary tract returned to normal after correction of the megalourethra. Early repair of megalourethra is therefore strongly advocated. The surgical technique used by all authors is based on Nesbitt's (1955) principles with only minor modifications; it has been found successful in all reported cases.

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Phimosis in Boys

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Summary—Phimosis, defined as scarring of the tip of the prepuce, was studied prospectively in a series of 23 boys aged 4 to 11 years. There was little to support the contention that the condition is caused by trauma, or by ammoniacal or bacterial inflammation of the prepuce, nor could any other aetiological factor be identified. Histological examination of the foreskin showed the appearances of Balanitis Xerotica Obliterans in 20 of 21 specimens submitted for study.

The usual reason for referral, and the commonest indication for circumcision, is "phimosis", but experience suggests that this condition is over-diagnosed and many unnecessary circumcisions performed in consequence. True, from its Greek derivation (φιμωσις, muzzling), the term might be applied whenever the foreskin cannot be retracted to reveal the glans penis, but Gairdner (1949) demonstrated that in young boys non-retractability of the foreskin is a normal finding and is due to the persistence of developmental adhesions between glans and prepuce. These break down spontaneously with the passage of time and, without interference, full retractability of the foreskin can be expected in almost all boys by their early teens (Oster, 1968). Non-retractability of this type requires no treatment and the term phimosis is best avoided in this situation since it implies the existence of pathology where there is none. On the other hand, there are cases where the tip of the prepuce loses its normal suppleness and becomes scarred, resulting in secondary non-retractability. The appearances are unmistakable (Fig. 1) and clearly pathological; we confine the term "phimosis" exclusively to cases of this type.

Little is known of this condition. Its aetiology has been variously ascribed to the trauma of forcible retraction (Twistington Higgins *et al.*, 1951), to ammonia dermatitis (Robarts, 1962) or to repeated episodes of bacterial balanoposthitis (Campbell, 1951). Its natural history is unknown and its histological features have not been described. That circumcision is the only possible treatment has never been questioned. In view of this lack of knowledge we elected to study a series of cases in detail.

Patients and Methods

A prospective analysis was made of 23 consecutive new cases of phimosis seen in the first 9 months of 1978. At the initial out-patient attendance full details of the history and physical examination were entered on a pro forma. All of the patients proceeded to circumcision, where the operative

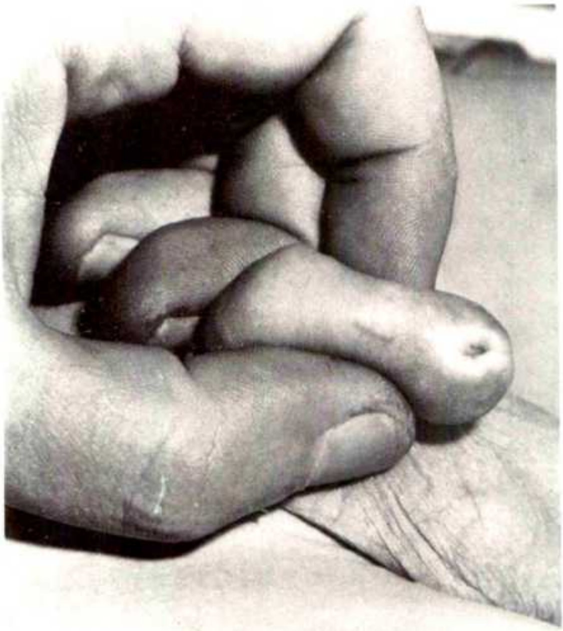

Fig. 1 The clinical appearances of phimosis; the white "scarring" of the tip of the prepuce is clearly seen.

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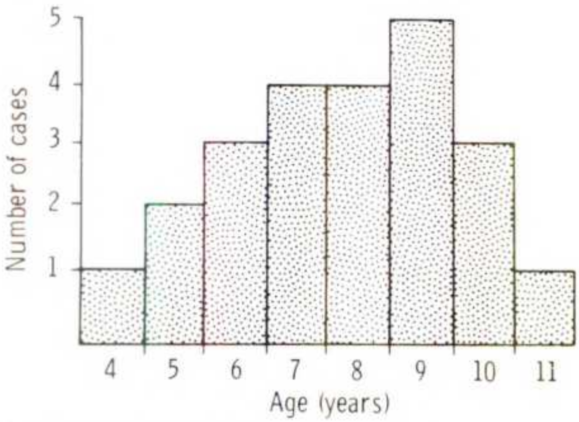

Fig. 2 The age of patients at presentation.

findings were noted, the urine and the bacterial flora of the prepuce cultured, and the operative specimen submitted for histological examination.

Results

Clinical Findings

The age distribution of the patients is shown in Figure 2. The mean duration of symptoms was 3.1 months (range 2 days to 14 months). Seven patients complained of poor urinary stream, 6 of dysuria, 4 of irritation or soreness of the prepuce, 2 of non-retractability of the foreskin and one of haematuria, whilst 3 boys admitted to no symptoms. One boy described a vesicular eruption on his prepuce at the onset of the disease, but in the remainder the process began insidiously. There were no apparent precipitating factors, nor any history of a change of clothing or washing methods. In 11 patients the foreskin had previously been fully retractile, in 4 partially retractile and in 4 non-retractile, whilst 4 patients had no recollection of the previous state of retractability of their foreskin. Five patients gave a past history of balanoposthitis, one of ammonia dermatitis and 6 of forcible retraction, but in each case the last episode of any one of these had been separated from the onset of phimosis by a period of years. All were fully continent by day and night. Two patients had a skin disease (psoriasis) and 3 an allergy (2 penicillin, 1 pollen). The fathers of 3 boys had been circumcised for reasons unknown. In a total of 14 brothers over the age of 5 years there were no instances of phimosis. All of the patients were prepubertal and physical examination was unremarkable apart from the presence of phimosis, which was confined to the tip of the prepuce and did not extend for more than 0.25 cm proximally.

Operative Findings

Adhesions between glans and foreskin were present in 6 cases and retained smegma in 2 cases. The underlying glans penis appeared normal except in one patient where there was a suggestion of involvement of the urethral meatus.

Laboratory Findings

An excess of leucocytes in sterile urine was found in one patient, but in the remainder the urine was free of bacteria or other abnormal constituents on routine laboratory testing. Pathogenic bacteria were cultured from the prepuce in 4 instances (*beta haemolytic streptococci* 2, *Proteus* 2). In other cases culture was either sterile or produced mixed growths of conventionally non-pathogenic organisms.

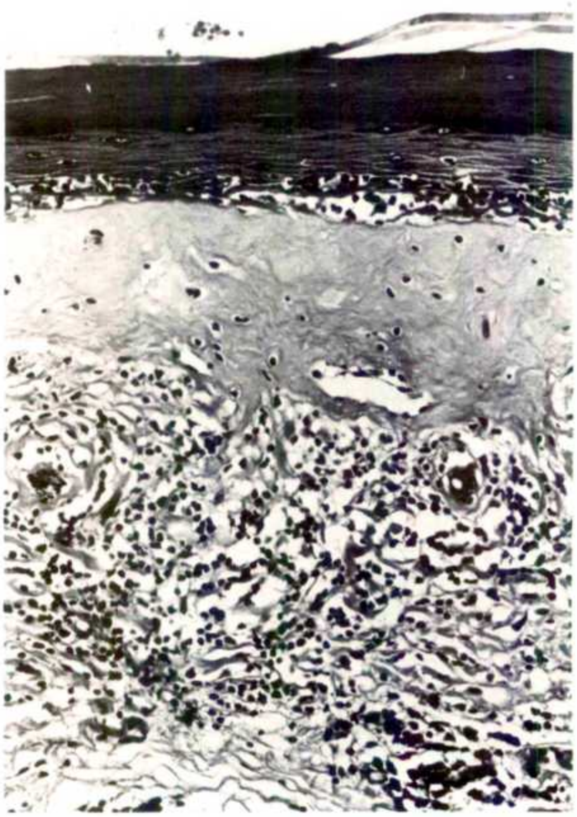

Fig. 3 Histology of the foreskin of a 7-year-old boy with phimosis, showing the features of BXO detailed in the text (H and E × 120).

Histological Findings

Twenty-one specimens were submitted for histological examination, all but one of which showed the features of Balanitis Xerotica Obliterans (BXO). The histological criteria for this diagnosis were oedema and homogenisation of collagen in the upper dermis, inflammatory infiltration of lymphocytes and histiocytes in the mid-dermis, atrophy of the stratum malpighi and hydropic degeneration of the basal cells (Bainbridge *et al.*, 1971; Lever and Schaumburg-Lever, 1975). A typical example is shown in Figure 3. The only atypical finding was that although the stratum malpighi was atrophic in some areas, other parts of the epidermis were of normal width or even acanthotic. A patchy non-specific outer dermal infiltration of chronic inflammatory cells was often present in other parts of the prepuce not affected by BXO. The single specimen not showing BXO had minimal chronic inflammatory changes in the outer dermis and marked dilatation of the lymphatic channels near the inner surface of the prepuce. The foreskins of 11 other boys aged 8 months to 11 years, who had been circumcised for religious reasons, were also examined histologically: none showed the changes of BXO.

Discussion

The findings of a previous survey (Rickwood, 1977) confirm that phimosis in the pathological sense is rarely seen in pre-school boys. Its aetiology remains obscure. Our data do not support previous contentions that it is due to forcible retraction, ammonia dermatitis or recurrent balanoposthitis. There appears to be no familial predisposition or any relation to the changes of puberty, nor is there evidence of its being a form of contact dermatitis, a local manifestation of general allergy or a reaction to retained smegma. It is not related to the presence or otherwise of preputial adhesions. If a bacterial organism is involved it is not a conventional pathogen. A viral aetiology remains a possibility.

The finding of BXO in almost all cases was unexpected, since this is a condition mainly reported in adults and childhood cases have been thought to be exceptional (Caterall and Oates, 1962; Schinella and Miranda, 1964; Mikat *et al.*, 1973; McKay *et al.*, 1975). BXO histologically resembles Lichen Sclerosus et Atrophicus, and may affect the prepuce (Bainbridge *et al.*, 1971), the anterior urethra (Staff, 1970) or both simultaneously. Although there are changes in the dermal collagen, there is no evidence that the condition is related to the general collagenoses (Lever and Schaumburg-Lever, 1975), and the notion that it is primarily an inflammatory disease is supported by the lymphocytic and histiocytic infiltration which is especially marked in its early stages (Staff, 1970). If so, however, the nature of the inflammatory agent is unknown.

It has been assumed that acquired phimosis persists or progresses. In this series, where all patients were circumcised within 2 months of presentation, no changes for better or worse were noted, but at a time when waiting lists were longer a few examples of spontaneous and apparently permanent regression were seen. On the other hand, in adult patients progression of the disease to involve the anterior urethra may occur, and the likelihood of this happening may possibly be increased as a result of circumcision (Stuhmer, 1928; Staff, 1970). The literature does not contain any examples of this occurring in childhood.

These considerations have some bearing on the management. Treatment is undoubtedly required, not only for the long-term problems associated with a permanently non-retractile foreskin, but because boys with phimosis are often much troubled with their present symptoms. Although spontaneous regression may occasionally occur, and although the changes of BXO have been reversed by the local application of topical corticosteroids (Caterall and Oates, 1962; Poynter and Levy, 1967), circumcision is undoubtedly the most efficacious treatment and there seems little reason to doubt its safety in the long term.

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Serum Hormone Levels in Patients with Malignant Testicular Germ Cell Tumours without Clinical and/or Radiological Signs of Tumour

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Summary — In patients treated for malignant testicular tumours without clinical and/or radiological signs of tumour, the following serum hormone levels were found:

In 15% of the patients there was a slight to moderate rise in luteinising hormone (LH) levels (up to 6 μg/l) due to increased pituitary gonadotrophin production; this was particularly evident soon after radiotherapy/chemotherapy.

In 50% of the patients there was a slight to marked increase in follicle stimulating hormone (FSH) levels (up to 11 μg/l), especially after radiotherapy/chemotherapy.

Serum testosterone levels were in the low range (up to 20 nmol/l) in the majority of the hemicastrated patients regardless of previous treatment.

A slight to moderate rise in serum oestradiol-17β and serum prolactin levels was noted.

During combination chemotherapy with vincristine, Adriamycin D, cyclophosphamide, actinomycin D and medroxyprogesterone acetate the serum testosterone levels were extremely low (below 6 nmol/l) with LH and FSH levels within the normal range. The decrease in testosterone levels was reversible after completion of the combination chemotherapy.

It is known that urinary and/or serum choriogonadotrophin (Wilson and Woodhead, 1972; Cochran *et al.*, 1975; Scardino *et al.*, 1977) as well as oestrogen (Cochran *et al.*, 1975) may be elevated in patients with testicular cancer. However, little is known about the serum hormone levels in patients who have undergone various forms of treatment and are without symptoms and signs of active disease. The aim of this work was to investigate the effect of unilateral orchiectomy, radiotherapy and/or intensive chemotherapy on the serum hormone levels in patients who have been successfully treated for testicular germ cell tumours.

Patients and Methods

Between 1 December 1976 and 30 June 1977, blood samples for hormone analysis were taken from 225 patients who were on chemotherapy or under regular follow-up at the Norwegian Radium Hospital following treatment for germinal testicular cancer. The mean age for the series was 34.8 years. In 182 of these patients there were no clinical and/or radiological findings of disease over a period ranging from 3 months to 10 years.

Diagnosis/Staging

Unilateral orchiectomy had been performed as part of the primary treatment in all patients. The tumours were classified histologically according to the WHO classification system (Mostofi, 1977) including both seminoma and non-seminomatous tumours. All patients had undergone clinical and radiological examinations (chest X-ray, inferior venocavography, pedal lymphography) in addition to routine blood tests, ESR, liver and kidney function tests as part of the initial diagnostic

Table Stage distribution (after hemicastration) in 182 successfully treated patients with testicular cancer

Stage	*No. of patients*
Stage I	142
Stage II	23
Stage III	17
All	182

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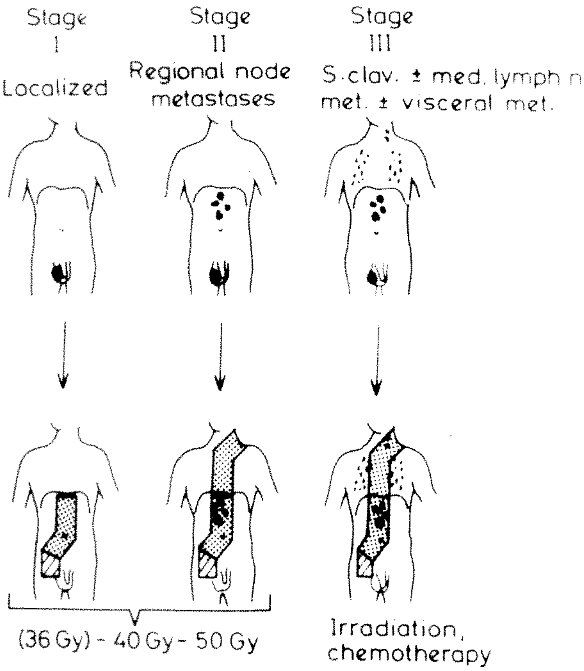

Fig. 1 Principles of staging and treatment in patients with testicular cancer at the Norwegian Radium Hospital between 1966 and 1977.

assessment. The table shows the distribution of the 182 patients in the various stages, based upon these examinations. Clinical examination, chest X-ray and blood tests were repeated at each attendance. More extensive X-ray examinations were performed only when clinically indicated. In all patients the remaining testis appeared normal to palpation during the observation period.

Treatment

Stage I Following hemicastration, high voltage radiation therapy to the para-aortic and ipsilateral iliac lymph nodes (40 to 50 Gy for 4 to 5 weeks) was given to 133 patients (Fig. 1). The ipsilateral inguinal lymph nodes were included in the radiation field if there were signs of infiltration of the testicular capsule or spermatic cord or if the patient had undergone surgery to the scrotum/groin region prior to hemicastration. The remaining 9 patients had non-seminomatous tumours and did not receive radiation treatment.

Stage II Radiation therapy was given following the same principles as in Stage I patients (Fig. 1). In addition, the left supraclavicular region and the mediastinum were irradiated.

Stage III Eight patients with lymph node metastases to the left supraclavicular region and/or to the mediastinum received radiotherapy to the same fields as Stage II patients. Nine patients with visceral metastases were treated by intensive combination chemotherapy including the following drugs: vincristine, Adriamycin, cyclophosphamide, actinomycin D and medroxyprogesterone acetate (VACAM) (Klepp *et al.*, 1977).

Hormone Analysis

As Cochran *et al.* (1975) have demonstrated that analysis of serum was more reliable than that of urine in detecting elevated choriogonadotrophin levels in patients with testicular cancer, analysis of serum has been used in the present study. Samples were taken from an arm vein between 8 a.m. and 2 p.m. and analysed for:

	Normal range
Luteinising hormone (LH)	<0.5 to 2.5 μg/l
Follicle stimulating hormone (FSH)	0.5 to 2.1 μg/l
Testosterone	12 to 40 nmol/l
Oestradiol-17β (E_2-17β)	0.04 to 0.11 nmol/l
Pituitary prolactin (PRL)	2 to 10 μg/l

The hormone determinations were performed by using specific radioimmunoassays (RIA) as previously described for LH (Sand and Torjesen, 1973; Torjesen *et al.*, 1974), FSH (Sand and Torjesen, 1973; Torjesen *et al.*, 1974), testosterone (Naess *et al.*, 1976), E_2-17β (Fosså *et al.*, 1977)

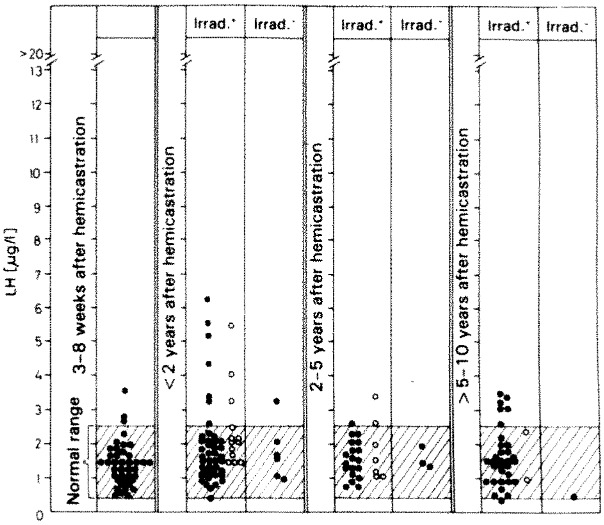

Fig. 2 Individual serum levels of luteinising hormone in 165 tumour-free patients treated by hemicastration ± irradiation (Stage I •, Stage II ○).

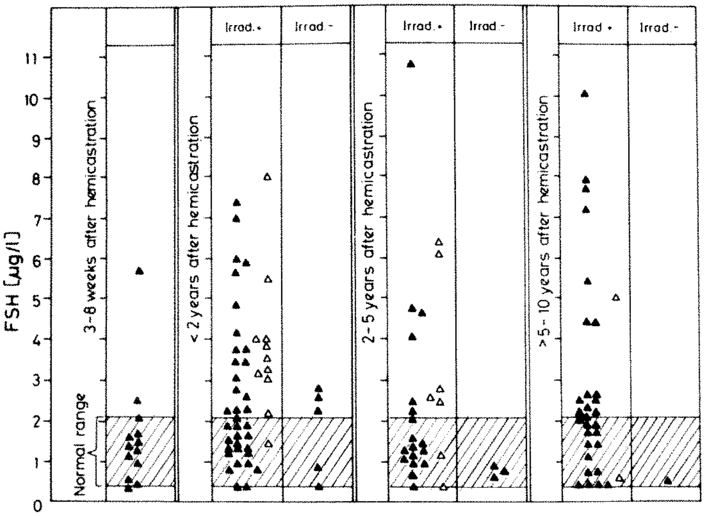

Fig. 3 Individual serum levels of follicle stimulating hormone in 134 patients treated by hemicastration ± irradiation (Stage I ▲, Stage II △).

and PRL (Rutlin *et al.*, 1977). The LH radioimmunoassay utilises an antiserum which reacts equally well with LH and tumour human chorionic gonadotrophin (HCG), as these 2 hormones differ from each other only by the β subunit. The present method therefore measures the sum of LH and HCG expressed as LH equivalent.

Statistics

Student's t-test was used to calculate the significance of differences between means.

Results

LH Figure 2 shows the serum levels of LH at various times after hemicastration given separately for patients with or without supplementary radiotherapy. Of 42 patients with Stage I disease 3 had slightly raised serum LH levels 3 to 8 weeks after unilateral orchiectomy. After irradiation a slight to moderate rise in LH levels was noted in about 15% of all patients during a 10-year observation period; it was seen most often in the first 2 years following hemicastration.

FSH Increased FSH levels were seen in 5 (out of 16) patients after hemicastration prior to radiotherapy and in about 50% of Stage I patients after irradiation. Such a post-radiation FSH increase was observed in 16 (out of 20) Stage II patients (Fig. 3). The post-radiation increase in FSH levels could not be related to inguinal irradiation (Fig. 4).

Testosterone Figure 5 shows the serum testosterone levels, most of which were in the low normal range (up to 20 nmol/l). Twenty-four patients out of 165 showed values below the normal range. In general, these findings remained unaltered during the observation period with the same tendency in both irradiated and non-irradiated patients.

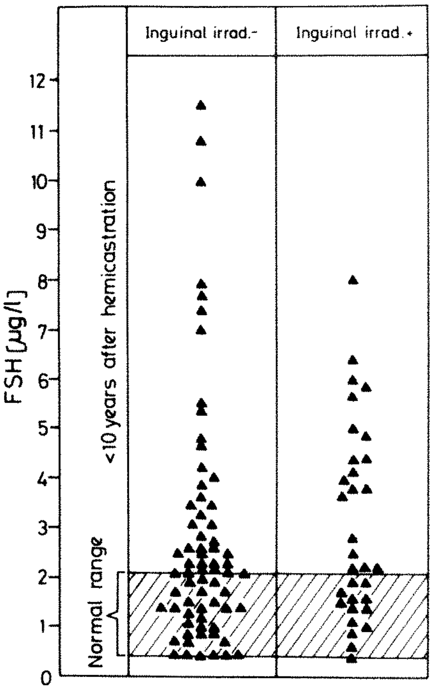

Fig. 4 Inguinal irradiation and serum levels of follicle stimulating hormone in 103 patients successfully treated (Stage I + Stage II).

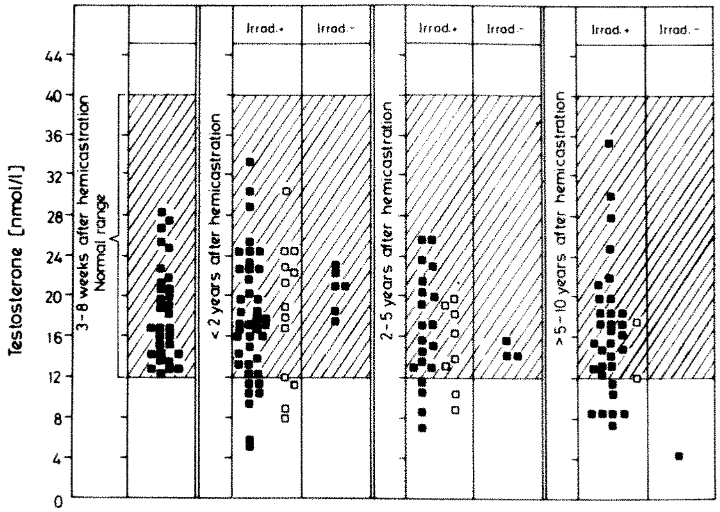

Fig. 5 Individual serum levels of testosterone in 165 tumour-free patients treated by hemicastration ± irradiation (Stage I ■, Stage II).

E_2-17β About half of the serum E_2-17β values were found in the upper normal range or slightly above (Fig. 6).

PRL Most of the prolactin levels were within the normal range, though incidentally raised levels were observed, especially shortly after radiation therapy (Fig. 7).

Effect of Chemotherapy

The serum hormone levels in 9 disease-free patients on VACAM chemotherapy are shown in Figure 8. In contrast to the non-chemotherapy patients, all patients had significantly reduced levels of serum testosterone ($P < 0.01$), while the levels of LH and FSH were normal. Only 2 out of 9 patients had elevated E_2-17β levels. The serum prolactin levels showed a slight to moderate increase.

Figure 9 demonstrates the serum hormone levels in 8 disease-free patients 3 to 6 months after completion of chemotherapy. Three patients had a slight to moderate rise in serum LH levels. The serum FSH levels were moderately to markedly increased in all patients. The serum testosterone levels were normal in 7 of 8 patients, though in the low normal range. The serum E_2-17β levels

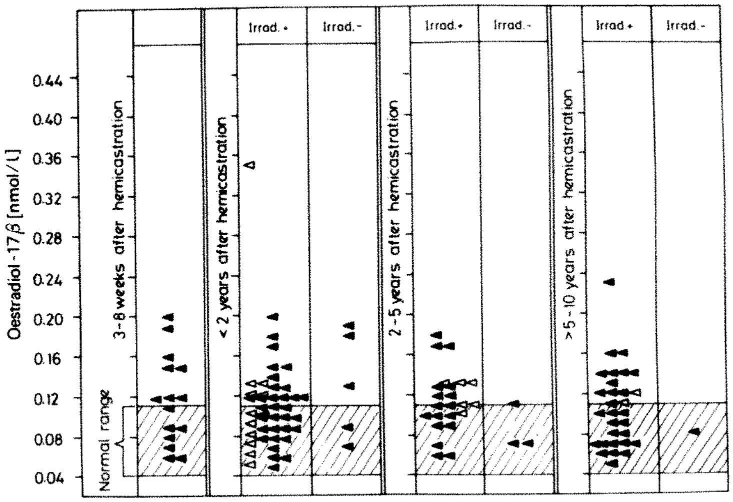

Fig. 6 Individual serum levels of oestradiol-17β in 128 tumour-free patients treated by hemicastration ± irradiation (Stage I ◀, Stage II ◁).

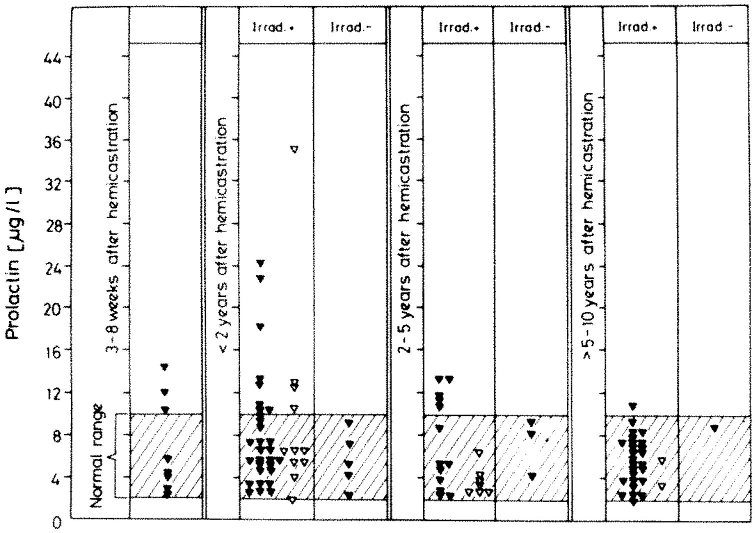

Fig. 7 Individual serum levels of prolactin in 111 patients treated by hemicastration ± irradiation (Stage I ▼, Stage II ▽).

were slightly to moderately increased in 5 out of 8 patients, whereas the serum prolactin levels were usually normal.

Discussion

It is commonly believed that in hemicastrated patients treated successfully for testicular cancer the remaining testis is able to maintain completely normal serum testosterone levels. Nevertheless, this study revealed testosterone levels in the lower region of the variation range in the majority of patients, even 10 years after treatment. It is unlikely that this testicular hypofunction can be explained by irradiation treatment and/or chemotherapy alone, as low testosterone levels were seen before radiotherapy/chemotherapy and in patients who did not receive irradiation/chemotherapy. It is also unlikely that the low testosterone levels are related to diurnal variations as more than 80% of all blood samples were taken before 11 a.m. Non-specific causes, such as stress or poor general health, can be excluded in these disease-free patients.

One aim of this study was to investigate the significance of elevated LH in patients apparently cured of their testicular cancer. Our results revealed incidentally and temporarily increased serum LH levels (up to 6 µg/l) in tumour-free patients. Though the LH RIA used in the present study

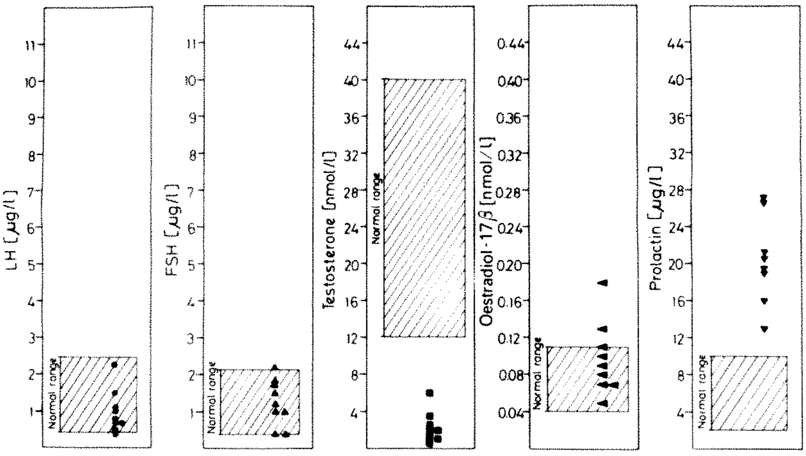

Fig. 8 Individual serum hormone levels during intensive chemotherapy (VACAM regime—see text) in 9 tumour-free patients.

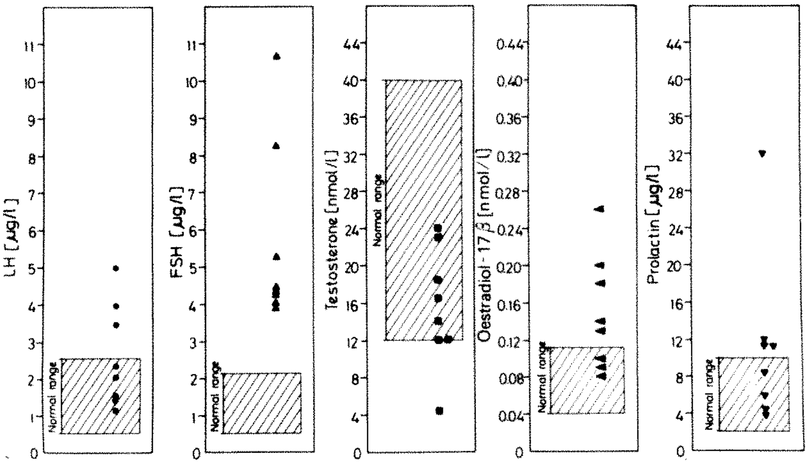

Fig. 9 Individual serum hormone levels in 8 tumour-free patients treated for testicular cancer (Stage III) 3 to 6 months after termination of intensive chemotherapy (VACAM regime).

includes HCG, the LH increase in the individual patient probably reflects increased pituitary LH production, as all patients remained tumour-free during the observation period.

The reason for this pituitary LH increase in disease-free patients may be the relatively low testosterone levels seen in many patients. However, raised LH levels were also found in tumour-free patients with normal testosterone values, especially shortly after radiotherapy/chemotherapy. These 2 forms of treatment seem, at least temporarily, to stimulate the hypophysis to increase LH production either by a direct effect on the hypophysis and/or indirectly by a reduced Leydig cell function during and shortly after radiotherapy/chemotherapy. The observation of subnormal testosterone levels and increased pituitary LH levels may also indicate a functional disturbance in the relationship between the pituitary gland and the Leydig cells in patients with malignant tumour and may be taken to support the hypothesis that testicular dysfunction is an aetiological factor in testicular cancer therapy (Mostofi, 1973).

Increased LH levels, as determined by the RIA used in the present study, may also reflect increased HCG levels produced by tumour cells (Wilson and Woodhead, 1972; Cochran *et al.*, 1975; Scardino *et al.*, 1977). In the individual patient, therefore, the finding of raised LH levels should be regarded as indicative of disease activity until excluded by supplementary clinical, biochemical and radiological examination. If possible, serum levels of tumour choriogonadotrophin (Vaitukaitis *et al.*, 1972) should be determined.

A moderate to marked increase in serum FSH levels (up to 11 µg/l) was observed in half of the tumour-free patients, especially following extensive radiation therapy in Stage II patients or after intensive combination chemotherapy. A marginal serum FSH increase was also observed in a few patients after unilateral orchiectomy prior to radiotherapy. There are 2 possible reasons for this: either primary dysfunction of the remaining testis or damage to the germinative epithelium by radiotherapy and/or chemotherapy. Under physiological conditions inhibin, produced by the germinative epithelium, suppresses the pituitary FSH production. As a result of a negative feedback the FSH production increases after damage to the germinative epithelium and reduced inhibin production (Setchell *et al.*, 1977). An increase in FSH has been found in patients treated by irradiation and/or chemotherapy for prostatic carcinoma (Fosså *et al.*, 1976) or malignant lymphoma (Asbjørnsen *et al.*, 1976a and b), probably due to a similar mechanism.

As regards the moderately increased E_2-17β and slightly raised prolactin levels in tumour-free patients, no obvious explanation has been found.

There are considerable endocrine side effects combined with the VACAM regime, in particular decreased sexual potency resulting from reduced Leydig cell function. This suppression of the Leydig cells is, however, reversible a few months after completion of treatment with VACAM and, according to the patients, sexual potency is restored within a few days after discontinuation of the drugs. It is probable that medroxyprogesterone acetate is responsible for the low testosterone values in patients on VACAM chemotherapy, as correspondingly low values are seen in patients with metastatic renal cancer treated with medroxyprogesterone acetate (Fosså, unpublished results). The suppression of Leydig cell function by high doses of medroxyprogesterone acetate is similar to that seen in patients with prostatic cancer during oestrogen therapy (Fosså *et al.*, 1977). It is not clear whether medroxyprogesterone acetate has a direct cytotoxic effect on the Leydig cells in addition to the inhibitory effect on the pituitary production of gonadotrophins. The observation that LH and FSH levels are decreased in tumour-free patients during VACAM chemotherapy indicates that reduced stimulation by gonadotrophins is a very important factor in Leydig cell hypofunction.

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Bilateral Germ Cell Tumours of the Testis

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Summary—Between 1952 and 1976, 760 men with testicular tumours were seen at The Royal Marsden Hospital. Of this group 21 (2.75%) developed tumours of the contralateral testis, in 2 instances synchronously and in the remaining 19 at intervals from 4 months to 15 years.

Of 15 men in whom adequate history had been obtained, 7 (46%) had a history of maldescent and in all 7 patients the pathology of both tumours showed the same histological subtype. Only one example of malignant teratoma undifferentiated (MTU) as first tumour was encountered; 13 of 19 (68%) patients had seminomas and the second tumour was a seminoma in 11 patients (58%).

Of the group of 21 patients, 12 (57%) are alive and disease-free. Of 14 Stage I patients (second tumour), 12 (85%) are considered cured of their 2 tumours. However, patients with evidence of extratesticular spread did badly, even if the second tumour was a seminoma, and treatment for these patients should include chemotherapy. Similarly, both Stage I MTU second tumours did badly.

It is well recognised that men who develop a tumour of the testis have an increased risk of developing a tumour of the contralateral testis, the quoted incidence ranging from 1 to 3.14% (Table 1). The Royal Marsden Hospital series has been examined to study the frequency and pathology of bilateral tumours, the relationship to previous testicular maldescent, and the treatment and prognosis of these patients. The present series excludes malignant lymphomas, which are the subject of a separate study (Duncan *et al.*, 1979).

Patients and Methods

Of 760 men treated for testicular tumours between 1952 and 1976, the details of 21 patients who developed bilateral tumours have been examined.

Histology and Staging

The classification of the Testicular Tumour Panel has been employed (Pugh, 1976). The following abbreviations are used:

Seminoma.
Malignant teratoma intermediate (MTI).
Malignant teratoma undifferentiated (MTU).

Details of patient investigation and staging have been described elsewhere (Peckham and McElwain, 1976). Since 1962 lymphography has been performed routinely together with intravenous urography and whole lung tomography.

The staging system is as follows:

I Tumour confined to testis, lymphogram negative, no evidence of metastases.
II Lymphogram positive but no supradiaphragmatic or extranodal metastases.
III Nodal metastases above and below diaphragm.
IV Extranodal spread (*e.g.* liver, lungs).

Alpha fetoprotein (AFP) and beta-human chorionic gonadotrophin (ß-HCG) blood levels were routinely monitored.

Table 1 Frequency of Bilateralism of Testicular Tumours

Author	*Total patients*	*Frequency of bilateralism (%)*
Hamilton and Gilbert (1942)	7000	2
Whittle (1957)	143	2.8
Stephen (1958)	100	3
Patton *et al.* (1960)	570	0.87
Blandy *et al.* (1970)	270	1.5
Testicular Tumour Panel (Pugh, 1976)	1812	3.14 (including lymphoma)
Present series	760	2.75

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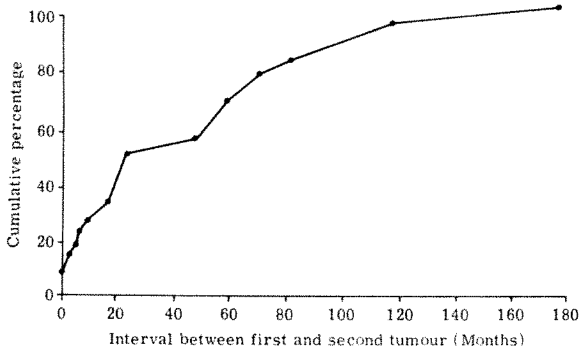

Fig. 1 Bilateral testicular tumours (excluding lymphoma).

Treatment

For Stage I and early Stage II patients orchiectomy and radiotherapy was the treatment of choice. In advanced Stage II and Stage III a drug-radiation-surgical approach was employed. Chemotherapy with or without whole lung irradiation was used in Stage IV (Peckham, 1976).

Results

Incidence

Twenty-one of 760 patients (2.76%) developed tumours of the contralateral testis either synchronously or sequentially.

Interval Between First and Second Tumour

Nineteen patients developed second tumours after intervals of 4 to 180 months (mean 53.4 months, median 48 months) (Fig. 1). In 9 patients (47%) the second tumour was diagnosed within 2 years of the first tumour and 13 (68.4%) in the first 5 years.

Two men, both presenting with Stage IV disease, had synchronous bilateral tumours. In one a right MTU and left seminoma were present and in the second patient both tumours were MTU.

Table 2 Relationship Between Histology of First and Second Tumours

Histology of first tumour	*Number of cases*	*Histology of second tumour*			
		Seminoma	*MTI*	*MTU*	*Unknown*
Seminomas	13	9*	2	2	–
MTI	5	2	3	–	–
MTU	1	–	–	–	1†
Total	19	11	5	2	1

* Elevated AFP and ß-HCG in 2 patients with subsequent histological diagnosis of coexisting teratoma at autopsy.

† Stage IV disease with elevated AFP and ß-HCG: orchiectomy not performed.

Histology of First and Second Tumour (Table 2)

Of the 19 patients with a sequential diagnosis of 2 primaries, the first tumour was a seminoma in 13 (68%) of cases.

Similarly, in 11 of the 19 patients (58%) the second tumour was a seminoma, in 5 (26%) MTI and in 2 (11%) MTU. Of the 13 patients with seminoma as a first tumour, 9 (69%) had seminoma as the second tumour, although in one patient teratomatous metastases were subsequently proven histologically. Only one example was encountered of a patient with an MTU as a first tumour; he presented with a second primary 3 years later. In this patient the diagnosis of the second tumour was clinical and orchiectomy was not performed since tumour dissemination was present.

The time lapse between first and second tumour in relation to histology of the second tumour is shown in Figure 2.

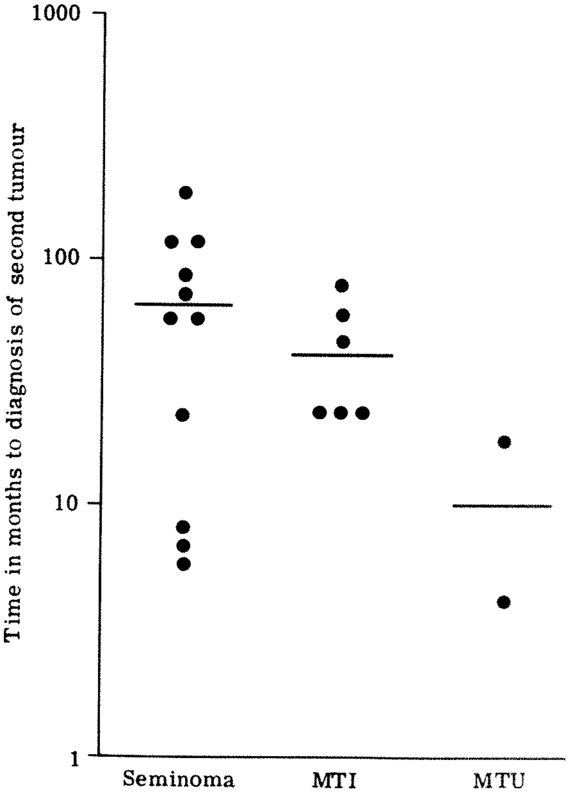

Fig. 2 Bilateral testicular tumours: interval between first and second tumour in relation to histology of the second tumour.

Table 3 Histology of First Tumour Related to Stage at Diagnosis of Second Tumour

Histology of first tumour	*Number of cases*	*Stage at presentation of second tumour*			
		I	*II*	*III*	*IV*
Seminoma	13	8	1	3	1*
MTI	5	5	–	–	–
MTU	1	–	–	–	1†
Total	19	13	1	3	2

* Elevated AFP—teratomatous metastases later confirmed.
† Elevated AFP and β-HCG—no orchiectomy.

Testicular Maldescent and Development of Bilateral Tumour

A history of previous testicular abnormality, including surgical correction for maldescent, was sought in 15 of the 21 patients: of these 7 (46.7%) had a history of unilateral or bilateral maldescent. Two were bilateral cryptorchids and 5 had unilateral maldescent. All 5 had right testicular maldescent and in 4 of these the first tumour had been on the right side. The interval between the first and second tumour in this subgroup of 7 patients varied widely from simultaneous presentation to 10 years.

All 7 patients with a history of maldescent had the same histological type in both tumours. These were bilateral seminoma 4; bilateral MTI 1; bilateral MTU 2.

Stage at Diagnosis of Second Testicular Tumours

Histology of the first tumour in relation to stage at presentation of the second tumour is shown in Table 3. Thirteen seminoma patients developed second tumours; of these 8 were Stage I after the second orchiectomy. Five MTI patients developed second tumours and all were Stage I on the second occasion. Histology and stage of the second tumours at presentation are shown in Table 4. Of the 11 patients who had seminomatous second tumours, 7 were in Stage I, one in Stage II, 2 in Stage III and the single Stage IV patient had elevated AFP, indicating non-seminomatous metastases subsequently proved histologically. All 5 patients who had MTI as second tumours were Stage I.

Table 4 Histology Related to Stage of Second Tumour at Presentation

Histology of second tumour	*Number of cases*	*Stage at presentation*			
		I	*II*	*III*	*IV*
Seminoma	11	7	1	2	1*
MTI	5	5	–	–	–
MTU	3	2	–	–	1†
Total	19	14	1	2	2

* Elevated AFP—teratomatous metastases later confirmed.
† Elevated AFP and β-HCG—no orchiectomy.

Outcome Following Diagnosis of the Second Tumour (Table 5)

Of the 21 patients, 12 (57%) are alive and 9 (43%) are dead. Of 18 patients who were initially Stage I or II at time of diagnosis of the first tumour, 12 (67%) remain alive and disease-free. All 4 Stage I MTI patients who developed a second tumour are cured. However, only the 7 Stage I seminoma patients were cured, and all 4 patients with evidence of extratesticular spread subsequently died. All 3 patients with MTU died, although 2 were only Stage I.

Treatment of Second Tumour and Cause of Treatment Failure

Of the 9 patients who died, 6 had Stage III or IV disease at the time of diagnosis of the second primary tumour. Both patients who had a Stage I MTU died of widespread disease at 18 and 36 months. A patient who had received irradiation for para-aortic nodal seminoma metastases 10 years previously reseeded into the retroperitoneal area from a second seminoma and died with extensive intra-abdominal disease.

Five patients who were in Stage I or II at second presentation received abdominal node irradiation. In one (seminoma) a low dose (1500 rad) was employed; full re-irradiation was employed in 3 patients and one had had a node dissection for

Table 5 Results of Treatment Related to Histology and Stage of Second Tumour

Histology of second tumour	*Stage at presentation*	*Number of cases*	*Alive*	*Dead*
Seminoma	I	7	7	–
	II	1	–	1
	III	2	–	2
	IV	1	–	1*
MTI	I	5	5	–
MTU	I	2	–	2
	II	1	–	1

* Elevated AFP—teratomatous metastases later confirmed.

the first tumour and was irradiated following the second orchiectomy. Two patients (both of whom remain disease-free) with small second tumours, and who were Stage I, had no treatment other than orchiectomy; a third patient was explored for an abdominal mass which was found to be a fully differentiated teratoma. He remains well at 5 years. Four patients received intensive combination chemotherapy but all subsequently succumbed to their disease.

Hormone Replacement

All patients received depot testosterone propionate (Primoteston Depot) (250 mg intramuscularly monthly) as soon as the second tumour had been removed.

Discussion

It has long been recognised that the patient who has had one testicular tumour is at increased risk of developing a second tumour of the contralateral testis, compared with the normal male population. In the present series 2.76% of men have had second tumours diagnosed, compared with the Testicular Tumour Panel's 3.14% (of 1812 patients) (Pugh, 1976). These figures are not comparable since testicular lymphomas have been included in the Panel's series and excluded from our own. In our own series the frequency of bilateralism in testicular lymphoma is 8% (Duncan *et al.*, 1979). If lymphoma and metastatic tumour are excluded from the Panel's series, there is a total of 27 patients with bilateral tumour of which 3 (11%) were simultaneous. This compares with 2/21 (9.5%) in the present series. If only the seminomas, teratomas and combined tumours are considered in the Panel's series, 25 cases of bilateral tumour were documented in a total of 1557 patients (1.6%). These figures are likely to be underestimates of the true potential for the development of bilateral tumours since the prognosis for Stage III and IV patients has been extremely poor and short survivals have allowed insufficient time for the second tumour to be manifest. Our figures indicate that the risk of developing a second tumour is increased at least 500-fold, compared to the general population. For this reason we believe that all testicular tumour patients should be followed for life.

It is of interest that in the present series, in almost half of those patients in whom a history had been recorded, there was a history of maldescent either bilateral or unilateral. Our observations agree closely with those of the Testicular Tumour Panel series where, of 57 patients with bilateral testicular tumours, 26 (45.6%) gave a history of maldescent. All 7 patients in the present series with a history of maldescent who developed second malignancies had similar histology in both tumours. This suggests that there may be a common systemic carcinogenic factor in these cryptorchid cases. Hamilton and Gilbert (1942) recognised an increased incidence of bilateral tumours with cryptorchids—to 15% for inguinal testes and 30% for abdominal testes.

The present observations agree with those of previous authors who have noted wide variability in the time interval between first and second malignancy. This varied from simultaneous presentations to 15 years in the present series, thus agreeing closely with the Testicular Tumour Panel's range of 0 to 16 years (Pugh, 1976), and again emphasising the need for long-term follow-up.

So far as histology is concerned, only one instance of a patient with an MTU as first tumour going on to develop a second tumour has been encountered, although approximately 70% of Stage I MTU patients are cured by orchiectomy and nodal irradiation (Peckham *et al.*, 1977). Sixty-eight per cent of first tumours were seminomas and 9/13 of the seminoma patients went on to develop seminomas as second tumours. This may be compared with the overall incidence of seminomas of only 40% of all testicular tumours (Pugh, 1976). In the Panel's series 11/14 seminoma patients who developed successive bilateral tumours had seminomas as their second tumour. This suggests that the chance of developing a second tumour is slightly higher with seminoma patients, which is at variance with the conclusions of Abeshouse *et al.* (1955).

The mean time to the diagnosis of a seminoma as second tumour was 67 months, for an intermediate malignant teratoma 42 months, and for an undifferentiated malignant teratoma 11 months. The number of observations is small but it is possible that time to the appearance of the second primary may be related to tumour growth rate, which in turn is related to histological subtype.

So far as prognosis is concerned, the numerical problem of a second tumour is a small one and 12 of the 21 patients in this group are cured of this disease. Of 14 Stage I patients 12 (85%) are cured. Thus the mortality due to second tumour is approximately 1% and considerably less than this for patients whose second tumours were Stage I. There is thus no justification for treatment policies which electively treat the remaining testis, since the probability of a second tumour is low, the probability of cure of the second tumour if it arises is good, and the chance of the patient remaining fertile following nodal irradiation is good provided high cord ligation has been performed in the appropriate manner (Thomas *et al.*, 1977).

So far as management is concerned, this depends upon accurate staging. If the second tumour has been detected early and if staging investigations, including tumour markers, are negative, no further therapy other than orchiectomy may be necessary, unless the tumour is undifferentiated. If there is evidence of abdominal node metastases and irradiation has been given for the first tumour, the prognosis has hitherto been bad even for seminomas. However, it is important to realise that the large majority of patients in this series were treated before the present era of accurate staging and more flexible treatment policies including, where necessary, combined chemotherapy, radiation and surgery. The treatment policy will depend on the histology. In seminomas re-irradiation may be practicable but, if metastases are present, therapy should include chemotherapy (Calman *et al.*, 1979). If the second tumour is a teratoma and metastases are demonstrated, intensive chemotherapy combined with surgical excision of bulky tumour and, in some cases, irradiation of supradiaphragmatic disease is the treatment of choice. Testosterone replacement therapy is an essential and effective component of patient management.

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Case Reports

Retrovesical Liposarcoma

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Case Report

A 34-year-old male complained of perineal pain. Rectal examination revealed a large, firm mass in the region of the prostate. Transperineal needle biopsy revealed a highly undifferentiated neoplasm presumed to be arising from the prostate. Radiotherapy with 3000 rads provided no relief and a repeat biopsy revealed a pleomorphic liposarcoma (Fig.). The patient underwent a total pelvic exenteration with pelvic lymphadenectomy. Histologically the margins of excision and the lymph nodes were free of tumour. He rapidly developed recurrences in the perineal wound and retroperitoneum and despite further radiotherapy and courses of Adriamycin he died within 3 months of the initial diagnosis.

Comment

Two more reports of retrovesical liposarcoma were culled from the literature (Edson *et al.*, 1961; Sheldon Polsky *et al.*, 1974), both occurring in young males. The prognosis of liposarcomas depends on their histology, being worst in the pleomorphic variety. The only surviving patient with retrovesical liposarcoma (Sheldon Polsky *et al.*, 1974) had a myxoid histology. The possibility of a retrovesical liposarcoma should be considered in young patients with large tumours in the vicinity of the prostate. A therapeutic approach combining radiotherapy, radical surgery and chemotherapy is suggested for the more anaplastic tumours.

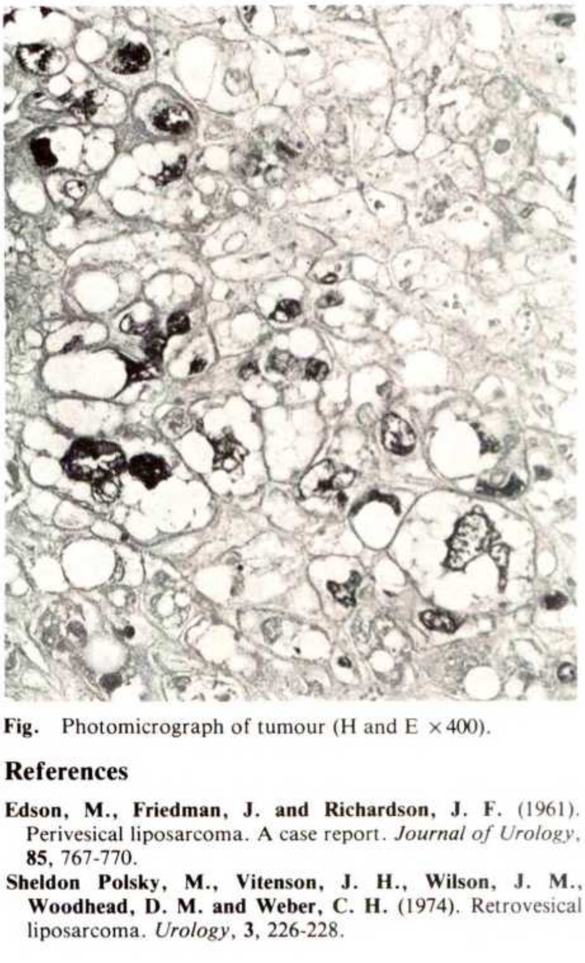

Fig. Photomicrograph of tumour (H and E ×400).

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Pubic Ectopic Testicle

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Case Report

The patient was a 45-year-old driver from Libya who had been referred for the investigation of infertility. He had been married for 23 years, had one son aged 14 and his wife had had at least one miscarriage 12 years previously. Sexual intercourse occurred regularly and without difficulty.

On examination he appeared to be healthy and normally masculinised. Examination of his genitalia demonstrated a pedunculated mass overlying the pubis and a single testis in the scrotum. The mass was the right testicle which was of normal size and consistency; it appeared to have a scrotum which emerged immediately above the dorsum of the penis in the midline (Fig.). The left testicle appeared to be normal.

Semen analysis showed azoospermia. Luteinising hormone, prolactin and testosterone assays were normal, but serum follicle stimulating hormone was raised (11.0 u/l). Biopsy of the ectopic testis demonstrated atrophy with a Johnsen score of 1.0. The left testicular biopsy showed focal atrophy with reduced spermatogenesis and a Johnsen score of 6.1.

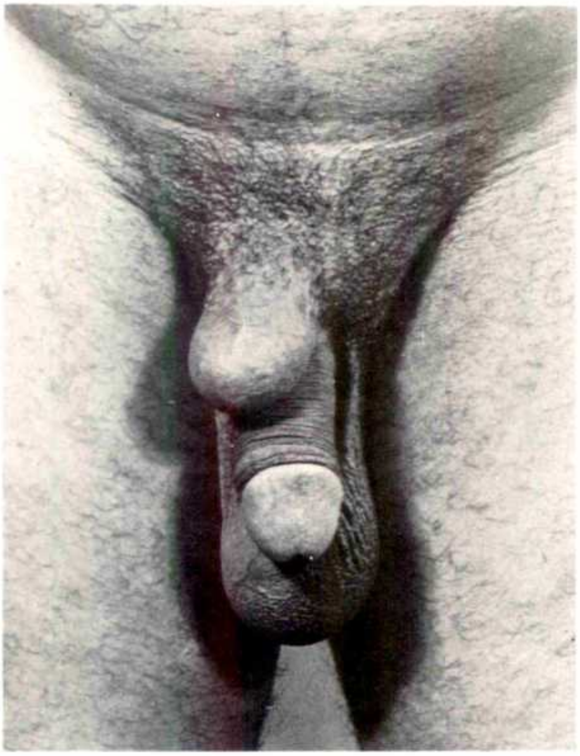

Fig.

Comment

When the testis has been deflected from its usual line of descent from the abdomen into the scrotum it is said to be ectopic. Both the testis and the scrotum on the affected side are usually well developed, in contrast to the incompletely descended testis where the scrotum is often poorly developed. Five ectopic positions are described (Campbell, 1970):

Superficial inguinal. This accounts for most cases of testicular ectopia.

Perineal. Only 132 cases have been reported (Campbell, 1970) and 13 testes in 988 cryptorchid boys were in this category (Gross and Jewett, 1956).

Femoral or crural. The testis lies in Scarpa's triangle and this is a rare anomaly.

Transverse. A rarity wherein both testes descend through the same inguinal canal to lie on the same side of the scrotum.

Penile or pubic. The testis is located at the base of the penis overlying the pubis or, as in this case, in a pubic pouch. Few authenticated cases have been reported of this condition and only one case has been reported with the ectopic testis on the dorsum of the penis (Raspall, 1949).

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Internal Urinary Diversion by a Percutaneous Ureteric Splint

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An indwelling ureteric splint, placed at cystoscopy, is an accepted means for temporary or permanent relief of lower urinary tract obstruction. Retrograde catheterisation of the ureter is technically difficult in a child and impossible in patients with recent ureteroneocystostomy, conduit diversion, ureterosigmoidostomy or malignant ureteric obstruction. The present case illustrated the feasibility of antegrade insertion of an indwelling splint. Our technique differs from that described by Goldin (1977) and is a hidden internal urinary diversion without need for external collecting devices and carries a lower infection rate than nephrostomy drainage. A steerable catheter proved to be especially useful in this procedure.

Case Report

A 5-year-old boy with a prune belly syndrome, urethral valves and renal dysplasia and megaureter underwent right nephrectomy immediately after birth. A U-tube nephrostomy was inserted into the left kidney. One year later a bladder neck incision according to Turner-Warwick was carried out. Four years thereafter urethral valves (Young type II) were noted and resected. Recurrent urinary tract infection during the ensuing 3 years prompted us to measure the pressure within the upper urinary tract via percutaneous nephrostomy (Whitaker, 1973; Günther *et al.*, 1977). At a perfusion rate of 10 ml/min there was an abnormal pressure rise of 70 cm H_2O. A Cohen antireflux reimplantation of the ureter, with tapering of the lowermost segment, was performed. After withdrawal of the splint an episode of pyelonephritis forced us to re-open the nephrostomy. Subsequently, antegrade splinting of the ureter was attempted. To overcome the ureteric kinks (Fig.) and the distal ureteric obstruction a Medi-Tech steerable catheter was successfully used. Leaving a J-guide-wire in place, the Medi-Tech catheter was removed. Aided by the guide a 6 FG polyethylene catheter perforated at both ends was inserted into the bladder while the proximal end was gently pushed into the renal pelvis using a short catheter. After removal of the J-guide internal urinary diversion was established and the percutaneous nephrostomy was removed. Injection of contrast material proved effective drainage through the splint.

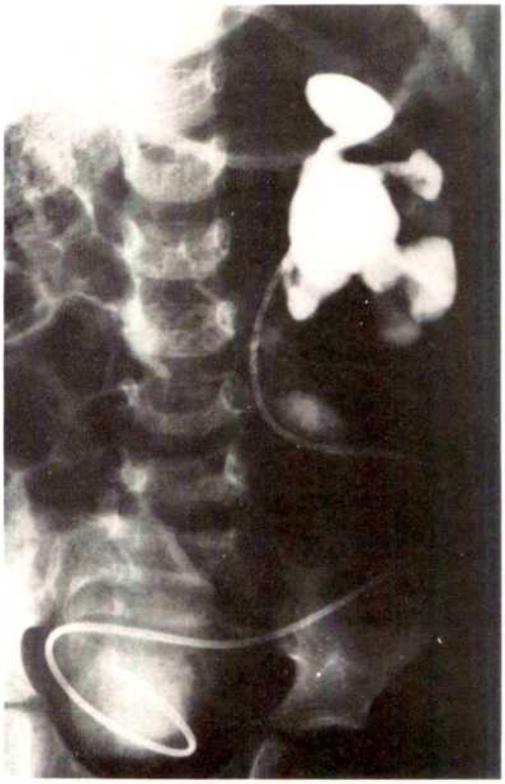

Fig. Internal drainage has been established by a percutaneously inserted indwelling splint; nephrostomy not yet removed.

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Author's Follow-up

Carcinoembryonic Antigen and Urological Carcinoma. A Review after 7 Years

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The name carcinoembryonic antigen (CEA) indicates the belief of those who first identified this glycoprotein that it occurred only in the presence of malignant or early fetal tissue. In addition, it was thought to be specific for endodermally derived carcinoma and that its measurement in the plasma would provide a diagnostic test for gastrointestinal cancer. Several reports soon showed that CEA was present in significant quantities in the plasma of patients with a wide variety of tumours, including carcinoma of the kidneys, urothelium and prostate.

Our investigations revealed significantly greater quantities of CEA in the urine of patients with urothelial carcinoma compared with other cancers and healthy control subjects (Hall *et al.*, 1973). Furthermore, positive urinary CEA tests occurred more frequently than positive plasma assays in urothelial carcinoma, even in T1S and T1 disease, thus raising the possibility of a urinary diagnostic test for bladder tumours.

For a tumour marker to be successful as a diagnostic aid it must yield a positive result in all patients with tumour with as few false positive tests as possible.

Experience with plasma CEA has shown conclusively that it is unreliable as a diagnostic test for cancer because a large proportion of patients, even with advanced malignant disease, yield normal results. In a few patients with advancing carcinoma, rising plasma CEA levels on serial testing may indicate metastasis before this is clinically evident, but few urologists would treat a patient on this basis alone (Coombes *et al.*, 1975).

The urinary CEA test has been evaluated in several hundred patients in a number of hospitals in the United Kingdom, other European countries and North America (Coombes *et al.*, 1975; Fraser *et al.*, 1975). The results have been uniformly disappointing, partly because of the high incidence of false negative results in the presence of demonstrable tumour (even the measurement of total 24-h urinary CEA did not reduce the false negative rate below 19% (Ionescu *et al.*, 1976)), and partly because of the very high proportion of false positive results caused by urinary infection and contamination by normal secretions from the vagina and ileal conduit mucosa.

Despite the possible improvements in the specificity of CEA assays by the recognition of variations in CEA molecular structure, this failure to distinguish between infection and tumour means that, at the present time, the measurement of urinary CEA does not make a significant contribution to the diagnosis or clinical management of urological cancer.

This is not to say that several years' intensive laboratory and clinical research have been in vain: a great deal has been learned about the immunochemistry of cancer. However, for the clinical urologist who seeks to simplify the diagnosis and follow-up of bladder cancer there is still no alternative to the well proven but invasive triad of cystoscopy, biopsy and bimanual examination.

References

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British Journal of Urology (1980), **52**, 167-168

Notices

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £500 for the best article in each volume of the *British Journal of Urology*. Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia, or South Africa; they must be undergoing urological training or have obtained consultant posts within 10 years of the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prize winner must submit a programme of visits to Urological Centres outside Britain for consideration by the Council.

European Association of Urology: Fourth Congress

Athens, Greece. 28-31 May 1980.

Round Table discussions will be held on:

(i) Surgical treatment of lithiasis.
(ii) New physical methods in urological diagnosis.

Further particulars from: Congress President, c/o Hellenic Promotion Organisation, 36 Voukourestiou Street, Athens 136, Greece.

Sixth Congress of Yugoslavian Association of Urology

Ohrid, Yugoslavia. 21-24 May 1980.

Official languages—English, French, German, Russian and Yugoslavian.

Further information from: Dr Lj. Vasilev, or Dr A. Stavridis, Surgery Clinic, Department of Urology, Vodnjanska 17, 91 000, Skopje, Yoglslavia.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

Edinburgh Urological Festival

Edinburgh. 1-3 September 1980.

A postgraduate course in urology for consultants, senior registrars and registrars. The topics to be covered include: unstable bladder, urethral syndrome, prostatitis, equivocal obstruction, upper and lower tract tumours, investigative techniques, calculi.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG, Scotland, UK.

32nd Meeting of the German Society of Urology

Berlin, Germany. 10-13 September 1980.

Further information from: Professor R. Nagel, Urologische Klinik der Freien Universität, Klinikum Westend, 1000 Berlin 19, Germany.

Canadian Urological Association: 1980 Annual Meeting

Banff, Alberta. 21-27 June 1980.

Further particulars from: Dr James O. Metcalfe, 421 Medical Arts Building, 11010 Jasper Avenue, Edmonton, Alberta, Canada T5K OK9.

Combined Meeting of BAUS and the Canadian Urological Association

Montreal, Canada. 21-25 June 1981.

In order to make provisional plans about transport and a short pre-congress tour, it is essential to have some idea of the number of British members likely to attend this meeting.

Any members of BAUS who are interested in attending should communicate with Mr J. L. Williams, Honorary Secretary, BAUS, Royal College of Surgeons, Lincoln's Inn Fields, London WC2, as soon as possible.

EORTC Urological Group—Current Clinical Trials (December 1979)

Multicentre cooperative trials are currently in progress for patients with kidney, bladder, prostate and testicular cancer. An outline of the various studies is given below for the benefit of any investigator who might wish to participate.

A. Studies on Kidney Cancer

Advanced carcinoma of the kidney with indicator lesions: a Phase II study testing the effect of methyl-GAG.

B. Studies on Bladder Cancer

1. *Superficial bladder cancer:* There are 2 studies to determine the effect of intravesical agents on recurrence rate:
    (*a*) Epodyl vs adriamycin vs control,
    (*b*) Thiotepa vs adriamycin vs cis-platinum.
2. *Infiltrating but operable (T3, M0) bladder cancer:* effect of adjuvant chemotherapy with adriamycin and 5-fluorouracil on survival and recurrence rate after cystectomy with or without pre-operative radiotherapy.
3. *Advanced bladder cancer with measurable lesions.* There are 2 Phase II studies:
    (*a*) Combination therapy with cis-platinum, adriamycin and cyclophosphamide (CAP),
    (*b*) Vincristine for those not suitable for the CAP study.

C. Studies on Prostatic Cancer

1. *A comparative trial of hormonal agents.* Two studies:
    (*a*) Stilboestrol vs estramustine phosphate,
    (*b*) Stilboestrol vs cyproterone vs medroxyprogesterone acetate.
2. A Phase II study for suitable cases with measurable lesions, using Vindesine.

D. Studies on Testicular Cancer—Non-Seminoma

Several trials, which each require participation from a number of centres, are available:

1. *For advanced testicular cancer:*
    (*a*) A comparison between 2 remission induction regimes, both containing cis-platinum,
    (*b*) A comparison of maintenance vs no maintenance chemotherapy after successful remission induction.
2. *For patients with limited lymph node metastases:* A comparison between chemotherapy and radiotherapy.
3. *For patients with advanced lymph node metastases:* A comparison between chemotherapy and radiotherapy vs chemotherapy alone.

Enquiries are invited for anyone interested in cooperating in any of these studies. Detailed information can be obtained from the coordinators of each study who can be contacted through the Secretary of the Urological Group (Mr Philip Smith, St James's University Hospital, Leeds, LS9 7TF, telephone Leeds 33144) or the Chairman (Professor Michele Pavone-Macaluso, 9 via Villa Trabia, 90141 Palermo, Italy).

First Meeting. Urological Days of Necker

Paris, France. 12-14 March 1981.

The topics are:

(1) Tumours of calices, renal pelvis and ureter.
(2) Ureteropelvic junction obstructive anomalies.

The mornings of 12 and 13 March will be devoted to televised operations. The afternoons of these 2 days and the morning of 14 March will be devoted to communications. Each speaker will have 30 minutes at his disposal and the lectures will be published as monographs by Masson.

Further information from: Secrétariat des Journées Urologiques de Necker, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

South African Biennial Urological Congress

Durban, South Africa. 10-15 August 1980.

Further particulars from: F. Nel, Hon. Secretary, The Urological Association of South Africa, P.O. Box 37287, Overport, 4067, Durban, South Africa.

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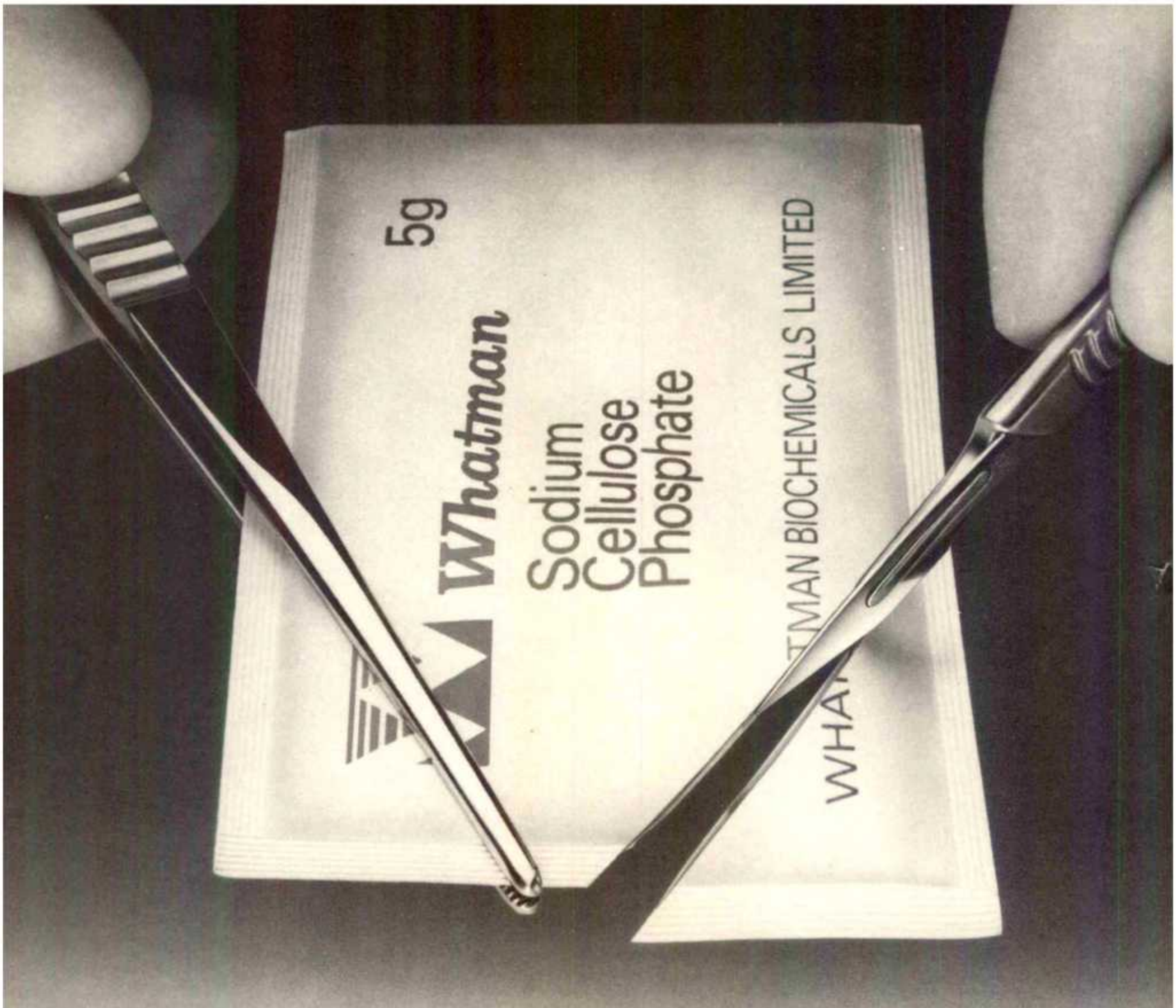

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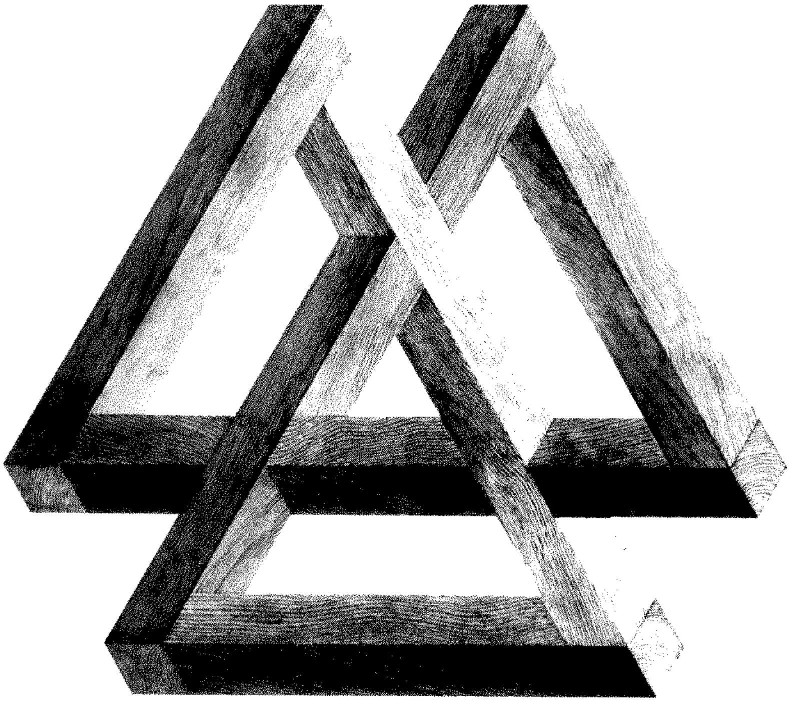

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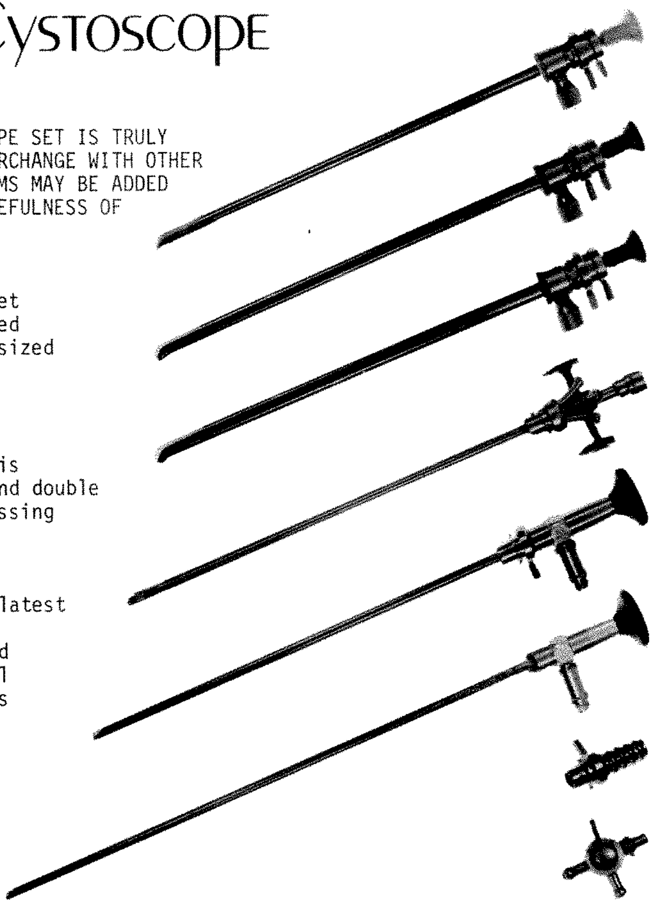

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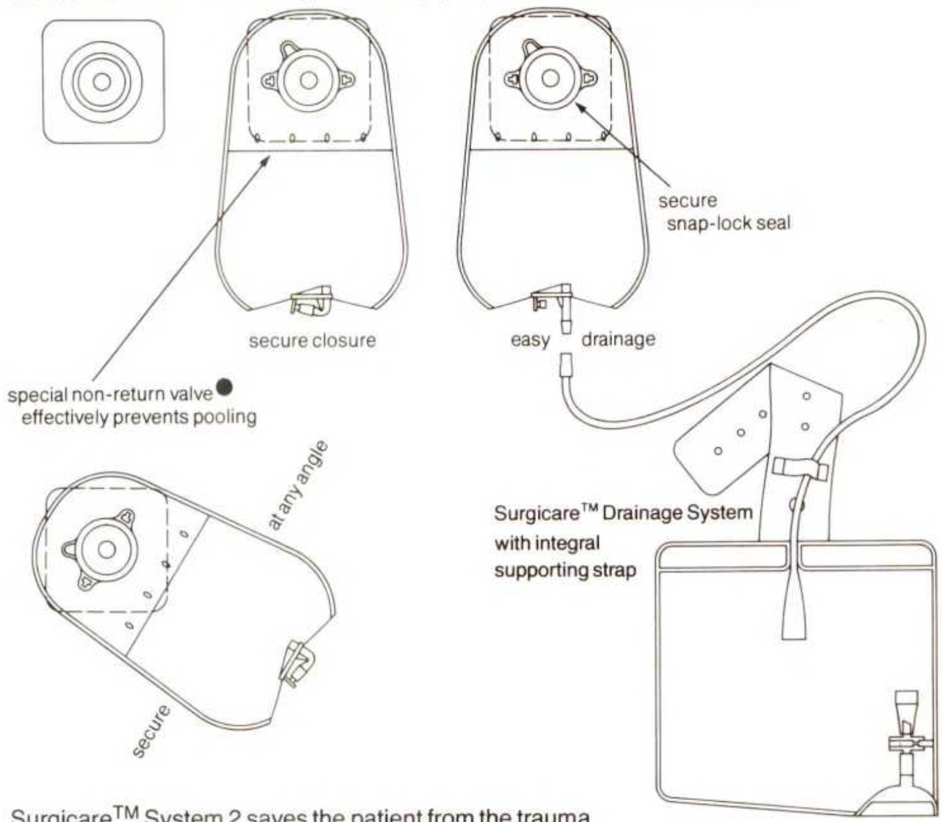

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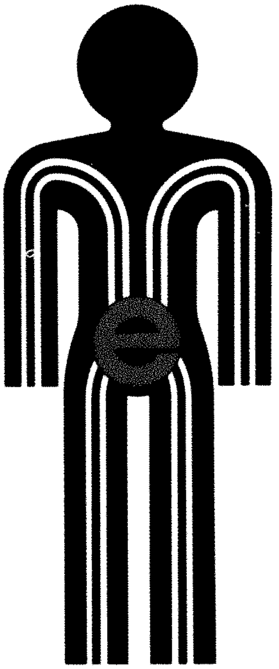

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P.A.No. 115/3/1

References
1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer. E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111; 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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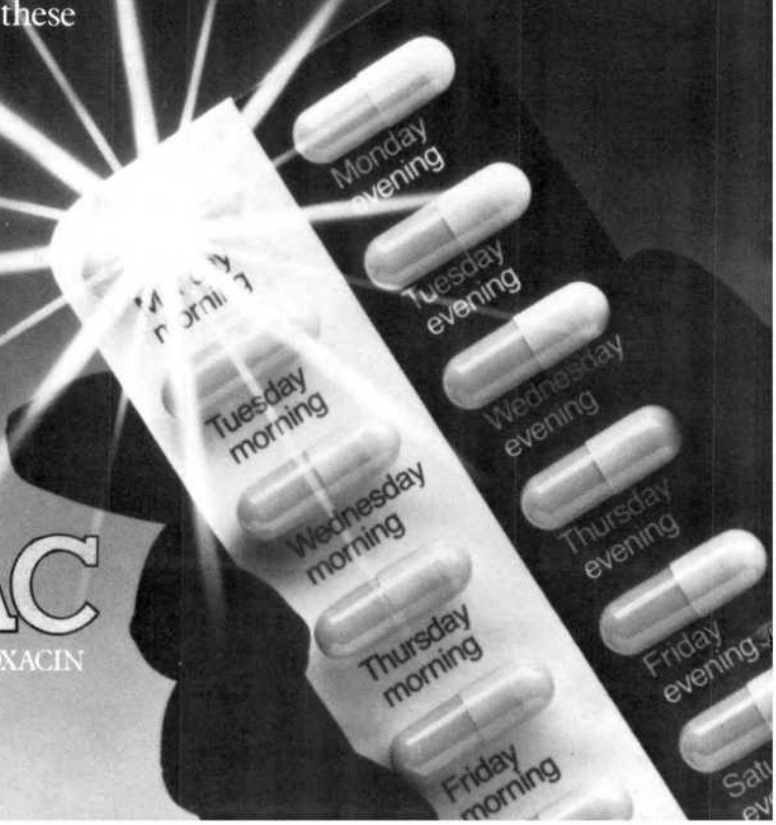

CINOBAC

CINOXACIN

Prescribing Information

"CINOBAC" Cinoxacin INN

Presentation

Capsules containing 500 mg cinoxacin INN PC.

Uses

CINOBAC is indicated in acute, recurrent and chronic upper and lower urinary tract infections due to susceptible micro-organisms.

Dosage & Administration

CINOBAC is administered orally. The usual adult dose is 1 g daily in two divided doses.

Contra-indications

Cinoxacin is contra-indicated in patients with a history of hypersensitivity to cinoxacin.

Warnings

The use of cinoxacin is not recommended during pregnancy, for the nursing mother, or for children as safety has not been established.

Precautions

CINOBAC is not recommended for patients with severely impaired renal function and should be used with caution in patients with reduced renal function.

Adverse Reactions

Gastro-intestinal – nausea, anorexia, vomiting, abdominal cramps and diarrhoea have been reported.

Hypersensitivity – rash, itching, urticaria and peripheral and oral oedema have occurred.

Other adverse reactions possibly related to cinoxacin include dizziness, headache, insomnia, tingling sensation, perineal burning, photophobia and tinnitus.

Transient changes in AST (SGOT), ALT (SGPT), BUN, ALP and creatinine clearance have been observed occasionally.

Product licence

PL 0006/0124

Price

Basic NHS price ex calendar pack 79p per day.

References

1. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), II, 1041. American Society for Microbiology, 1978.
2. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), I, 704. American Society for Microbiology, 1978.
3. Proceedings of the 9th International Chemotherapy Congress, 1976, 5: 417.
4. Antimicrobial Agents and Chemotherapy, 1976, 9: 502.

*Including patients with physical abnormalities of the urinary tract.

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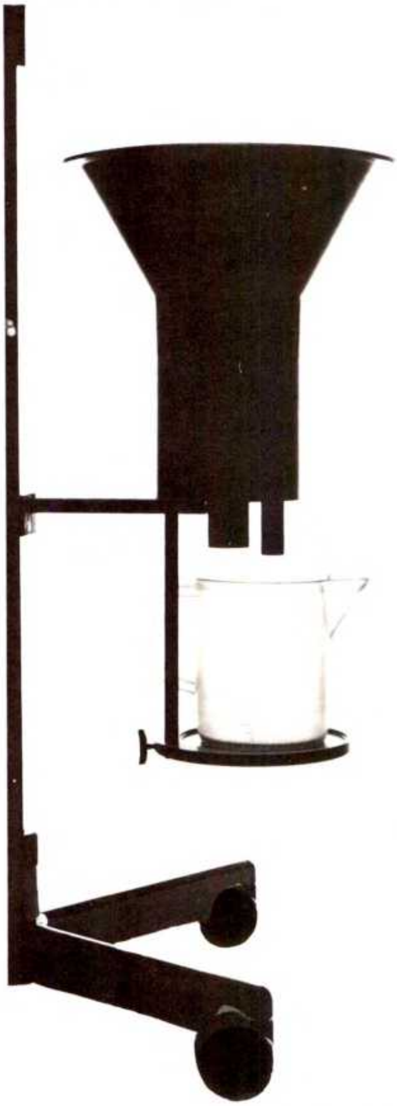

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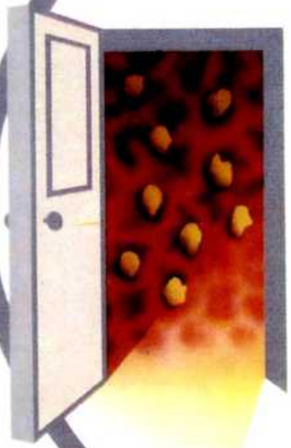

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Antibiotic	Overall Success
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Cephalexin	62%
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Trimethoprim	**96%**

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In a study on recurrent U.T.I.'s
"... trimethoprim is the most effective of the antibacterial agents examined."[3]

Greater efficacy with fewer side effects.

In the trial in acute U.T.I.'s

"... the total side effects caused by ampicillin, cephalexin and co-trimoxazole were similar and occurred twice as often as when trimethoprim was given alone ..."[2]

Antibiotic	No. of Patients	% Side Effects
Ampicillin	88	22
Cephalexin	84	25
Co-trimoxazole	83	21
Trimethoprim	**84**	**8**
Total	339	

Prescribing information

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Ipral is indicated for the treatment and prophylaxis of acute and chronic urinary tract infections.

Actions
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Dosage and administration
For acute urinary tract infections 2 tablets twice daily is recommended. For long term and prophylactic therapy 1 tablet twice daily is recommended.

Contra-indications
Ipral should not be given to patients with severe renal insufficiency where blood levels cannot be monitored regularly. Ipral should not be used in pregnancy or during the first few weeks of life.

Precautions
Care is necessary in administration to patients with impaired renal function. Special precaution should be exercised in patients with a predisposition to folate deficiency.

Side-effects
Nausea, vomiting and skin rashes may occur but are rare. Ipral may depress haematopoiesis during prolonged therapy. This has proved reversible when treated with calcium folinate.

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"Treatment with TMP (trimethoprim) alone is superior to the combined regimen due to a smaller incidence of side-effects; ..." thus "... introduction of TMP alone on the market is recommended."[4]

"Less gastrointestinal side-effects and skin rashes have occurred with trimethoprim ..."[3]

References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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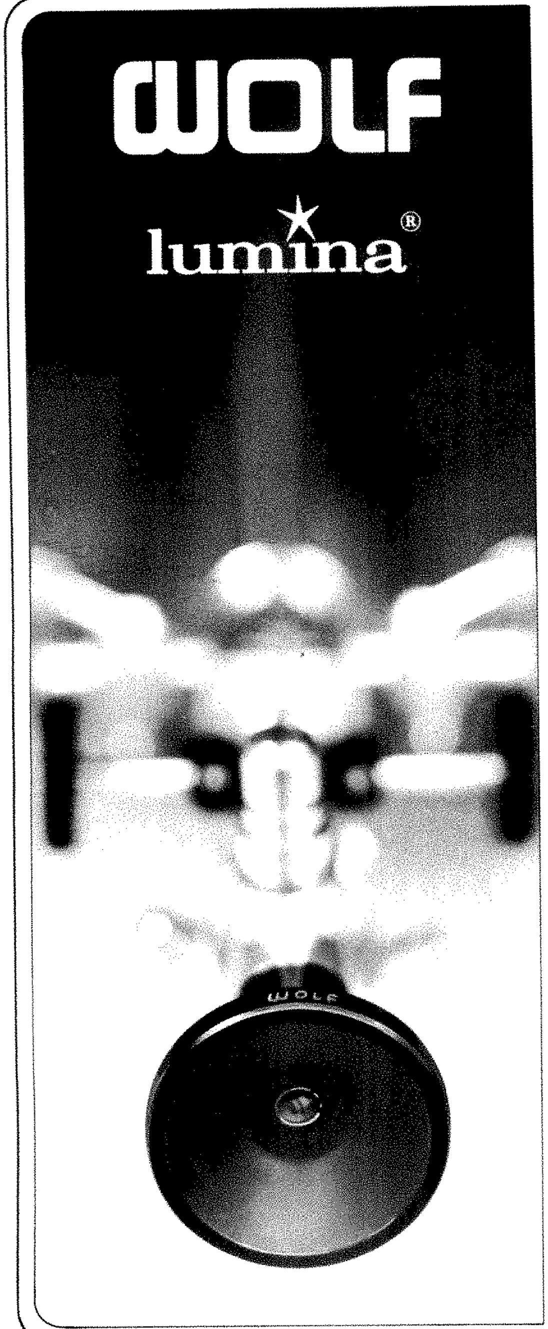

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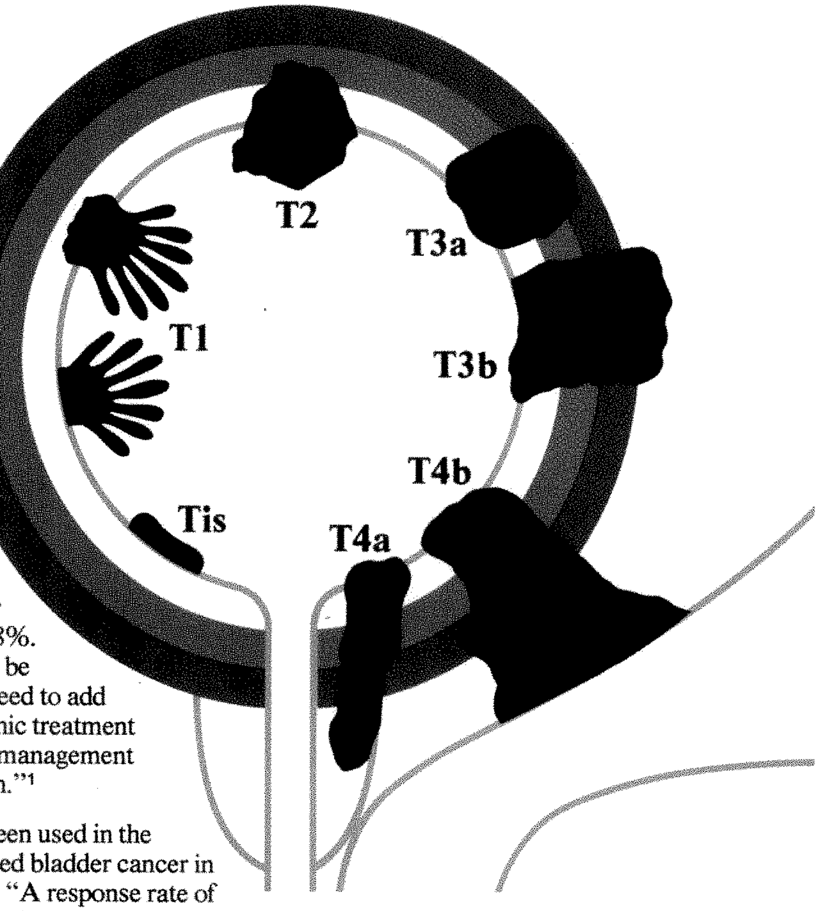

The 5-year survival of patients with T2/T3 bladder cancer is only 16-28%. "If the results are to be improved then we need to add some form of systemic treatment to the conventional management of the primary lesion."[1]

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1. *Brit. med. J. 1977, 2, 1562*
2. *Brit. J. Urol. 1977, 49, 673*
3. *Cancer Res. 1977, 37, 2771*

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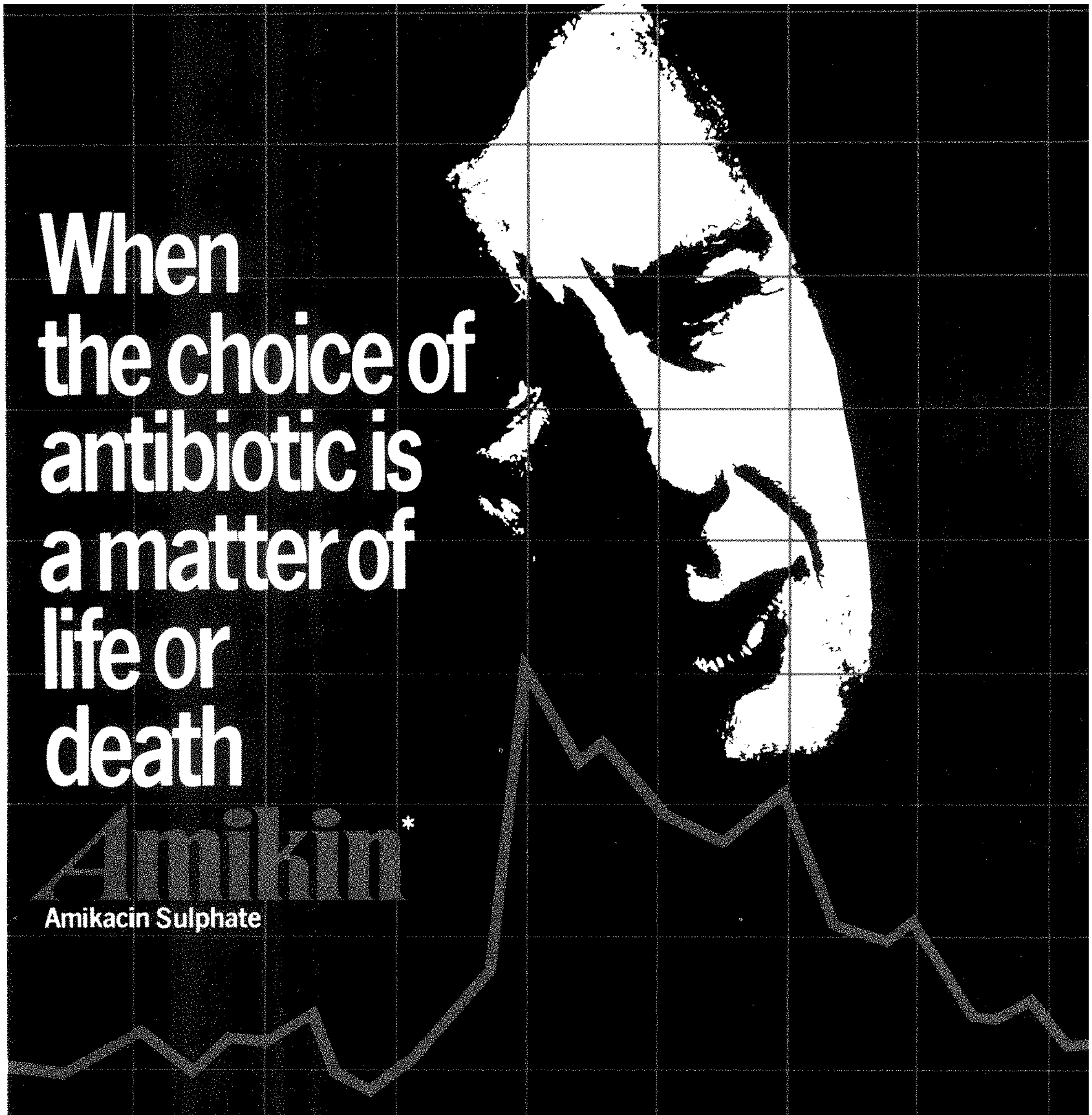
Dosage and Administration *ramuscular or intravenous administration* For most fections the intramuscular ute is preferred, but in life-hreatening infections, or in patients in whom ramuscular injection is not feasible, the intravenous route, either slow bolus (2-3 minutes) or infusion (30 minutes) may be used. *lts and children* 15mg/kg/day in two equally divided ses. Use of the 100mg/2ml rength is recommended for children for the accurate measurement of the ppropriate dose. *Neonates and premature infants* An al loading dose of 10mg/kg ed by 15mg/kg/day in two equally divided doses. *Life eatening infections and/or e caused by pseudomonas* The adult dose may be ased to 500mg every eight hours but should neither exceed 1.5g/day or be administered for a period longer than 10 days. A ıaximum total adult dose of 5g should not be exceeded. *Impaired renal function* In atients with impaired renal ction, the daily dose should educed and/or the intervals etween doses increased to d accumulation of the drug. *ntra-indications, warnings, etc.* Patients should be well hydrated during AMIKIN therapy. In patients with impaired renal function or diminished glomerular ltration, AMIKIN should be used cautiously. In such ents, renal function should be assessed by the usual ethods prior to therapy and iodically during therapy. As ith other aminoglycosides, ototoxicity and/or hrotoxicity can result from use of AMIKIN; precautions on dosage and adequate ration should be observed. e use of AMIKIN in patients with a history of allergy to noglycosides or in patients may have subclinical renal or eighth nerve damage ced by prior administration ephrotoxic and/or ototoxic gents should be considered caution, as toxicity may be additive. In these patients MIKIN should be used only if, in the opinion of the physician, therapeutic advantages outweigh the potential risks. The risk of otoxicity is increased when IKIN is used in conjunction with rapidly acting diuretic rugs, particularly when the diuretic is administered intravenously. Such agents include frusemide and acrynic acid, which is itself otoxic agent. Irreversible deafness may result. **Pregnancy**: The safety of IKIN in pregnancy has not yet been established. **Side effects**: When the mmended precautions and dosages are followed the ncidence of toxic reactions, ch as tinnitus, vertigo, and partial reversible or irreversible deafness, skin rash, drug fever, headache, paraesthesia, nausea and iting is low. Urinary signs of irritation (albumin, casts, and red or white cells), zotaemia and oliguria have reported. AMIKIN, should ot be physically mixed with ther antibacterial agents in ges, infusion bottles or any her equipment. Each agent should be administered separately. *Legal category* 1. **Product licence numbers** KIN PAEDIATRIC Injection 100mg/2ml 0125/0087. IKIN Injection 500mg/2ml 125/0092. **Basic NHS cost**



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References:

1. Walker JM, *et al., J. Antimicrob. Chemother.* 1979; 5:95-99.
2. Reynolds AV, *et al., Brit. Med. J.* 1974; 3:778-780.

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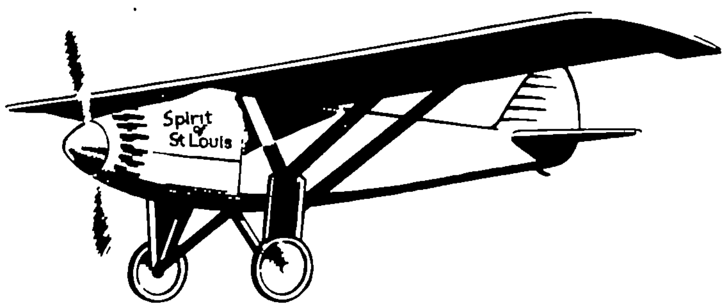

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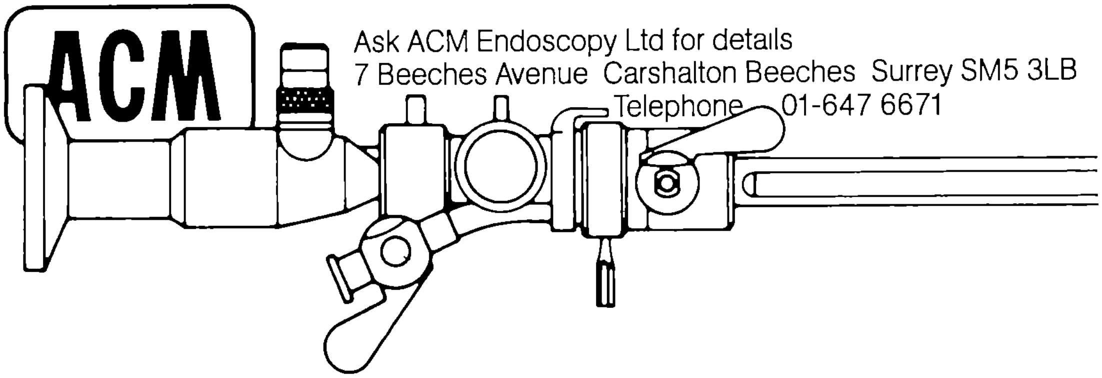

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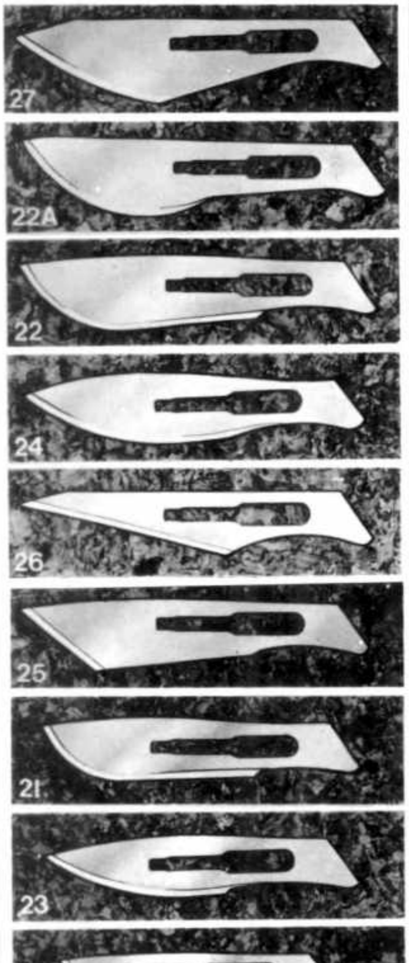

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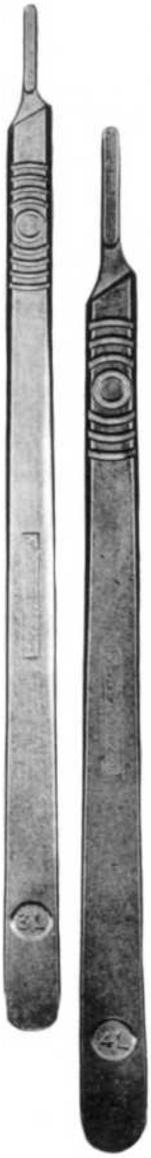

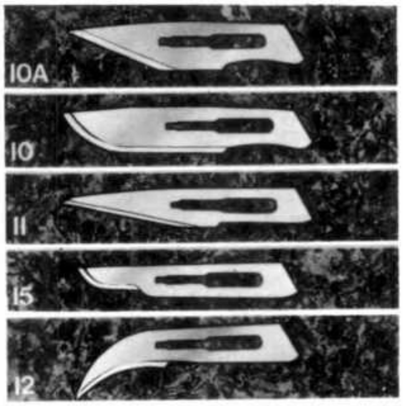

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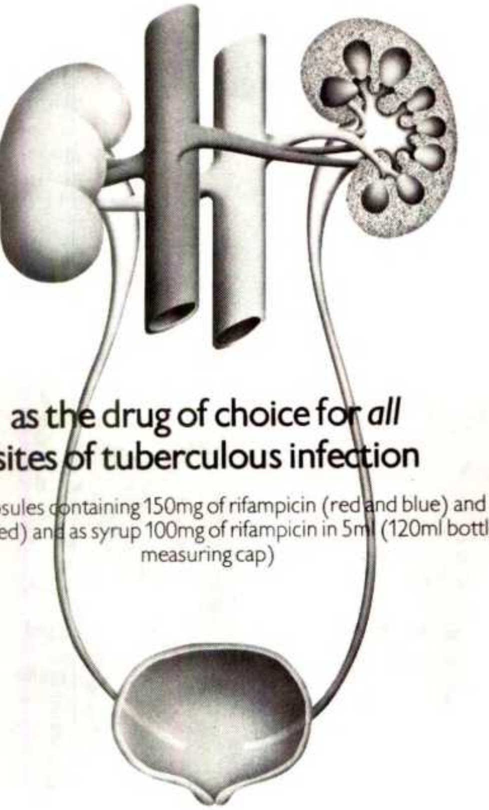

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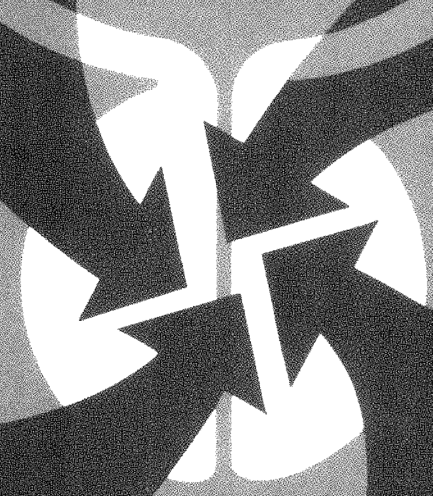

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Presentation: Orange, film-coated tablets each containing the equivalent of 100mg of minocycline. **Indications:** Bronchitis, Sinusitis, Prostatitis, Salpingitis and other infections caused by susceptible strains of Gram-positive and Gram-negative organisms including some tetracycline-resistant strains of Staphylococci. **Dosage:** Adults only – 2 tablets initially followed by one tablet b.d. **Contra-indications:** Known hypersensitivity to tetracyclines, systemic lupus erythematosus. **Precautions:** Use with caution in patients with hepatic or severe renal dysfunction; absorption of MINOCIN is impaired by concomitant administration of preparations containing calcium, magnesium or aluminium but not by food or milk in moderate quantities. **Warnings:** The use of MINOCIN may occasionally result in overgrowth of resistant organisms and, during tooth development may cause discolouration of teeth. **Side-effects:** Nausea, vomiting and occasionally dizziness. **Legal category:** P.O.M. **Package quantities:** Packs of 9 and 45 tablets. Code 5334. **Basic NHS Price:** [illegible] 9, £3.35, 45, £15.73. **Date of preparation or last review:** June, 1979.
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Lederle Laboratories Division of Cyanamid of Great Britain Ltd., Fareham Road, Gosport, Hants. PO13 0AS. (Tel: 0329-[illegible])

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British Journal of Urology (1980), **52**, 169-173
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Report of the Standing Committee on Urological Instruments: Solid State Diathermy Generators

J. P. MITCHELL (Chairman), J. P. BLANDY, J. G. GOW, C. H. KINDER, G. N. LUMB, R. REES and R. T. TURNER-WARWICK

The Standing Committee on Instruments for the British Association of Urological Surgeons was requested to investigate the qualities of surgical diathermy machines equipped with transistors rather than valve oscillators. These machines appeared on the market for the first time about 4 years ago and many different types have been developed since then. At the time of starting this investigation there were 9 on the market in the United Kingdom and it was, therefore, the intention that all of these should be tested by each member of the Instrument Committee.

The authors of this report are indebted to Mr Eric Charlton Edwards of Manchester and Mr John Williams of Sheffield, who were the successive secretaries during this period of study. Mr John Withycombe was with the Committee at the beginning of the investigation but resigned on his retirement from practice in this country.

All 9 distributors of the diathermy machines which claimed to be transistorised were informed of the plans for this investigation and they agreed to bring their machines to each of the hospitals in which the members of this Committee practised for a period of 24 to 48 h testing in use. The ninth distributor declined to accept our invitation as he felt that his machine was already too highly priced to be acceptable on this market and that this exercise would not be profitable. The machines tested were supplied by the following distributors: (1) Thackrays Ltd; (2) Eschmann Bros and Walsh; (3) GU, all from the United Kingdom; (4) the Diadone distributed by Downs Surgical Ltd; (5) the Neomed distributed by Rimmer Bros; (6) the Valley Lab distributed by Cardiac Recorders; (7) the Erbotom by Rank, Stanley Cox; (8) the Siemens machine. The Committee wishes to express its gratitude to these 8 distributors and manufacturers for their very valuable co-operation in bringing these machines to various hospitals at the request of each individual tester at a time convenient to the hospital and to the urological surgeon concerned.

With the introduction of the transistor, some manufacturers found it possible to simplify the diathermy generator to a single circuit in which the wave form could be manipulated to produce 3 different patterns corresponding to coagulating, cutting and blending respectively. In earlier machines, using valve or spark-gap oscillators, there were usually 2 circuits—one a valve oscillator for cutting and the other either a spark-gap circuit or a spark-gap simulated circuit for coagulation. In these machines the blended current was obtained simply by operating the 2 circuits synchronously, with the result that the patient was submitted to a summation of the power output of both circuits at the same time. Despite the introduction of the transistor, it has been found that some manufacturers still use a double circuit and summate the 2 currents. Other manufacturers, as already mentioned, have succeeded in simplifying the circuitry by using a variation of the wave form for each of these 3 functions.

In recent years it has also become apparent that the safest way to make sure that the plate electrode is making adequate contact with the patient is to isolate the diathermy circuit from any earthed contact, so that when the plate has not been applied to the patient adequately the diathermy generator will not operate. This system has been described variously as the "isolated circuit", the "earth-free circuit", "isolated earth", a "floating earth", etc. In principle this means there is no risk of leak of current via a metal contact area on the operating table or attached to it, so that the current can return to the earth terminal of the diathermy machine. The risk of a thermo-electrical burn should therefore be considerably reduced. This principle conflicts with all previous ideas of earthing every object in the operating theatre to a common earth point. Although the Safety Officers of the Department of Health and Social Security have not officially recognised this form of earthing, no official objection has been raised and this

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

has generally been taken as unofficial recognition and acceptance.

Since then, however, it has been shown that even though the circuit is isolated, if the plate accidentally makes contact with another earthed object, such as the pedestal of the table or the earthed cabinet of the diathermy generator (Mitchell, 1979), then the whole system can operate and the patient would once again be at risk for a thermo-electrical burn. The commonest resting place for the plate electrode when not in use is on top of the diathermy machine. Therefore, this risk is more than just a hypothetical hazard and one of the recommendations that this Committee would endorse is complete insulation of the top of the diathermy cabinet.

It now appears clear from work carried out with various transistorised diathermy generators that it is the interruption of the continuous sine wave into short bursts of current which provides the coagulating effect. The shorter the burst and the longer the time interval, the better the coagulation. The longer the burst and the shorter the time interval, the more cutting effect is produced. The blending on single circuit diathermy is a wave form mid-way between the coagulating and cutting pattern.

The assessment of the function of these diathermy generators when tested in use must be accepted as very much a subjective impression and, as has been found on previous tests of diathermy machines, the impression that various surgeons have of the performance of one machine as compared to another is certainly not absolutely consistent. It is only fair to say that all machines produced effective diathermy both for cutting and for coagulating. A detailed pro forma was filled in by each surgeon who tested each diathermy.

Therefore, despite anything that this report may state, it is still essential that every surgeon should test a diathermy machine himself before making his final decision to purchase. It should also be stated that this investigation was intended primarily to assess the use of diathermy under water for endoscopic purposes and less attention was paid to the function of the machine for open surgery.

Difficulty was experienced using the German-made machines, since they were fitted only with the Continental fittings for the cables. A series of adaptors had to be constructed which could readily convert the Continental fittings to the conventional fittings found in this country. This, however, should not be taken as criticism of the German machines as they were, in fact, conforming to the proposed EEC standards.

Considerable variation was found in the power output from different dial readings, which were anything but linear. For example, the Eschmann TD 300 was extremely sensitive to minimal adjustment of the volume control. At its setting of 5, cutting was adequate, at 5.5 it was excellent, at 6 there was such marked arcing that the loop would disintegrate within one or 2 operations of transurethral resection. On checking the volume control against power output curve, it was seen that the curve was rising steeply between the settings of 4 and 6. It is understood that this has been adjusted in the newer machines, since the Eschmann TD 300 was investigated for this report. Similarly, in the GU Solstar, little change in the output occurred from the setting 2 to 5.

Certainly the transistorised machines appear to cut under water much more effectively than the old valve oscillator machines, but there was in some instances considerable gas production. Gas production depends on a variety of factors which at present are ill understood, and further investigation in this field is required. Two members of the Committee had the impression that the GU Solstar produced less gas but other members remained unconvinced, so perhaps it was a local factor in the water or in technique.

In order to monitor the activity of the machine so that it cannot possibly activate inadvertently, some noise should occur during operation. When valve oscillators first replaced spark-gap for cutting, the machines became silent and around 1958 the manufacturers began to add a monitor which gave audible evidence of activity. Of the machines tested in this trial, all except the Siemens machine produced an audible hum to indicate when the footswitch was activated. In the Siemens machine, this audible monitor is only an optional extra which the Committee agreed unanimously should be mandatory. Most of the machines have a different noise for cutting and for coagulating, but in most cases when the blend current was used the tone was the same as the cutting monitor. Most of the Continental machines had a noise suppressor control which, in certain instances, could reduce the noise so that it was virtually inaudible. In certain instances the switch was easily accessible and any member of the staff in the theatre could adjust the diathermy so that the machine made no noise at all. This was regarded as unsafe.

When testing for the isolation of the circuit, it was found that the GU Solstar, although transistorised; was not in fact an isolated circuit and was operating at a frequency too high for isolation but, as a conventional earthed circuit, it worked satisfactorily. The original machine presented by Thackrays proved not to be a solid state generator at all, but their new machine, the Nova 2, which has appeared on the market in recent months, is in fact a true solid state isolated circuit. Unfortunately, this Nova 2 machine was not available in time to be tested by all members of the Committee before this report was prepared. All other machines tested proved to be solid state and reacted as though they were isolated circuit. The Valley LAB SSE 3b, which is the latest of the machines from this company, still has an earthed circuit but monitors the contact of the indifferent electrode to the patient by the differential between the current passing on the active electrode and the current passing on the indifferent plate cable. Any wide variation indicates that the current is passing via an alternative pathway back to the diathermy generator and immediately the machine is tripped. This device has a patent right exclusive to Valley Lab.

Most theatre staff today are familiar with the alarm monitored circuit to ensure continuity of the plate to the diathermy machine. As soon as this circuit is broken an intolerable howl develops on the machine, lasting until the fault is corrected. With the introduction of the isolated circuit, some manufacturers felt that they could safely dispense with this plate monitoring. After discussion of this point, the Committee recommended that manufacturers should continue to monitor the earth circuit irrespective of the introduction of the earth-free diathermy system. With the uncertainty of the future of the isolated circuit and the patent rights held by Valley Lab on their effective method of monitoring the patient plate contact, it was felt unwise to withdraw this monitoring precaution on the plate cable at the present time.

Despite the small size of the machine and the limited number of controls necessary, it is surprising how complex some of the control panels had already become. The Siemens and Erbotom test machines were both labelled in German, but the new machines on the market are now in English. It was felt that only the British-made machines were labelled clearly and in a manner that would not confuse the nursing staff. A clear and simple panel is essential for the safety of this equipment as in the UK it is often the junior nurse in the theatre who is asked to switch on the diathermy. The addition of the bipolar circuit tended to make the panel more confusing as, for example, in the Eschmann TD 311, whereas without the bipolar the TD 300 was an extremely simple panel to understand.

The indifferent electrodes varied considerably in design. The Erbotom was expensive and looked like a piece of chain mail; the Siemens was also expensive, but all machines could be used with the standard GU dry plate, which is one of the cheapest of all indifferent electrodes.

Most of the machines were provided with alternative designs of foot pedal. Part of the reason for this was the insistence of the Department of Health and Social Security on the use of the round insulated rubber pads which many urologists find very stiff to operate from the sitting position. The consensus of opinion of the Committee was that the piano pedal type of footswitch is infinitely preferable as it is easier to control and requires a lighter foot touch. The relative position of the cut and coagulation pedals came in for discussion as Mr Turner-Warwick drew the apt analogy of the accelerator and brake pedal on our cars when he insisted that the cutting pedal should be on the right and the coagulation pedal on the left—in other words the reverse of the arrangement both in America and, more recently, on the Continent. Diathermy panels have recently been altered by agreement with the DHSS so that they correspond to the position of the foot pedals. It seems likely, however, that the surgeons will lose the day on this decision as the officials at the DHSS and the manufacturers between them have decided to provide the diathermy for the American and Continental markets without reference to the users in this country. However, it should be said that most of the manufacturers were prepared to supply either the piano pedals or the DHSS round foot pad and if users in this country prefer to accelerate or cut on the right and brake or coagulate on the left, then they were quite prepared to supply the piano pedal in that arrangement. One of the easiest footswitches to operate was on the Diadone 400, which used pneumatic pedals. These have also been introduced for the new Thackray Nova 2, but their effectiveness with the passage of time could not be tested.

If any air leak occurred then, of course, the footswitch could be rendered useless. However, as tested, it was easy to control, had a light touch and despite its light weight did not slide around the floor. The fact that this dispenses with any electrical cable meant that the footswitch was completely safe for any of the staff to handle.

Although the different surgeons have varying indications for the use of the blending current, nevertheless it was thought that this was an essential part of a modern diathermy generator. Hence it was surprising to find that the Siemens Radiotom 700 had no blend circuit. Users were recommended simply to press both pedals simultaneously. Most of the machines offered only one setting of blend current, with the exception of the SSE 3 ValleyLab, which offered 2 settings, and the Neomed, which offered 3 settings. This may, in certain instances, be an advantage.

The Committee did not set out to assess the bipolar diathermy facilities, but as the testing progressed many took the opportunity of using the bipolar attachments when they were provided. In most instances the bipolar circuit is an optional extra. The use of bipolar forceps is a technique which requires a little understanding; it operates satisfactorily only with exactly the same volume of tissue between the blades on each occasion and, of course, is not applicable to endoscopic work as yet. Most members felt that the small additional outlay on the initial cost of the diathermy generator to have a bipolar circuit is well worthwhile.

Radio interference was noted in neighbouring theatres with the use of all of these generators. Interference with ECG monitors is bound to occur unless special radio frequency suppressor chokes are used in the leads. The ordinary resistors used at present are not sufficient to control this interference. At the same time, such suppressors would obviate the risk of a burn at the site of contact of an ECG electrode.

The Table gives the prices at the time of going to press. These prices are quoted in sterling. Anyone purchasing diathermy is advised to be very cautious regarding the price quotation and to ensure that, in fact, it includes the footswitch and the noise monitor, as both of these items are sometimes quoted as extras, though the diathermy will not operate without a footswitch and should never be used without the noise monitor. All of the German and American machines were found to perform with complete satisfaction but, of course, their prices do not compare favourably with their British-made counterparts.

Table Diathermy Machine Prices*

		1979 (Nov.)
1. Diadone 400 (Downs Surgical) now replaced by Diadone 450 with bipolar output included		£1590.00
2. TD 300 (Eschmann)		£1394.99
3. Thackray Nova II		£1550.00
4. GU Solstar		£1275.00
5. Valleylab	SSE2K	£1795.00
(Cardiac Recorders)	SSE3B	£2695.00
6. Erbotom (not supplied without bipolar)		£1753.90
7. Radiotom 704 (Siemens)		£1757.00
8. Neomed (Rimmer)		£1837.50

Bipolar output is available with all machines.
* All prices exclusive of VAT.

A similar investigation is being carried out in Cardiff under the auspices of the DHSS, but it is understood that this will be covering only 3 or 4 of the new transistorised diathermy generators. The other machines being investigated will be the conventional valve oscillators.

Since presenting this report at the 1979 BAUS meeting, only one comment has been received from other users, apart from those already on the Committee. This was a testimonial for the Martin diathermy, *i.e.* the machine from the one manufacturer who declined to join the investigation because the machine was considered to be too expensive on the UK market. Although the Martin appears to be an excellent machine, it has in fact no blend unless the operator presses both pedals simultaneously. In this respect it is comparable to the Siemens Radiotom.

This report is not intended to be a *Which?* purchasing guide, but it is advisable to ensure that servicing facilities are available within the area, even though with the new Solid State machines it is unlikely that regular servicing is going to be necessary. Most faults seem to become evident very early on and would still be covered by warranty.

A word of warning to those in the Middle East or in the Indian subcontinent: it is important to ensure that the mains current is reasonably stable. Fluctuations ranging from 90 to 300 volts on the mains have been recorded, which cause havoc with any diathermy generator and, in particular, the solid state transistorised machine.

The members of this Committee hope that this report will be accepted as constructive rather than destructive criticism. Such features as the need for insulation on the top of the cabinet, the risk of suppressing the audible monitor of activity, the simplicity of the control panels, the facilities of bipolar and handswitch operation, the monitoring of the earth cable, possible improvements in the grip of the footswitches on wet theatre floors, and a good useful servicing manual as well as a simple operating leaflet, are all features to which we would draw the manufacturers' attention. Further improvements in the future that could be recommended are: standardisation of the electrode cables and sockets; a reduction in the gas production with underwater cutting, a more even increment with changes in the dial settings, and research into the problems of fading after prolonged resection.

Advances in these machines are occurring so frequently and so rapidly that any firm recommendation for one machine or the other could very well be completely out of date by the time this report is published. Suffice it to say that all machines cut and coagulated adequately and it is hoped that from this report both purchasers and manufacturers will have a clearer guide on the features to check when considering the purchase of this equipment.

Finally, the authors of this report wish to extend a profound word of thanks to all of the manufacturers for their extremely helpful co-operation in this investigation.

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The Advantages of ^{99m}Tc DTPA(Sn) in Dynamic Renal Scintigraphy and Measurement of Renal Function

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Summary—The results of excretion urography (IVU) and dynamic renal scintigraphy using ^{99m}Tc DTPA(Sn) were compared in 109 urological patients.

Computer analysis of the gamma camera data provided a reproducible, accurate, qualitative and quantitative assessment of renal function and was found to be superior to urography in the detection of morphological defects of the renal parenchyma and in the identification of early upper tract obstruction. The radio-isotope study is a safe, non-invasive investigation, easily performed on an out-patient basis, requires no prior preparation and is without significant radiation hazard to the patient.

Despite the limitations of the excretion urogram (IVU) it remains the primary diagnostic procedure in the investigation of the urological patient. However, it provides only a qualitative examination of the renal tract. In recent years both qualitative and quantitative assessment of glomerular function and renal tract morphology using technetium^{99m} labelled chelates have become possible with the development of gamma camera linked computer systems (Hauser *et al.*, 1970; Britton and Brown, 1971; Klopper *et al.*, 1972; Ayre-Smith and Blake, 1976; Nielsen *et al.*, 1977; Macleod, 1978).

These techniques are complementary and enhance the value of the final opinion (Davies, 1976). However, the questions that arise are: (1) To what extent is the information increased above that obtained from the standard IVU examination? (2) Can radionuclide investigations of the kidney be substituted for conventional radiology in some circumstances?

In an attempt to answer these questions a comparative study was carried out in patients requiring investigation for urological symptoms in whom renal function was assessed by routine IVU and gamma camera processed technetium ^{99m}DTPA(Sn) scintigraphy.

Patients and Methods

One hundred and nine urological patients were investigated by means of the standard excretion urogram examination and computer processed ^{99m}Tc DTPA(Sn) scintigraphy performed in sequence. There were 79 male and 30 female patients whose ages ranged from 16 to 84 years (mean 44.6). The data from 217 kidneys have been examined.

Excretion Urogram (IVU)

Intravenous urography was performed using a dose of 0.5 to 1 ml/kg body weight of "Urovison" (Schering) contrast medium.

^{99m}Tc DTPA(Sn) Nephrograms

Following an intravenous injection of 0.5 to 1 mCi of ^{99m}Tc DTPA(Sn) the patient's kidneys were monitored for 1000 s using a gamma camera interfaced to a Varian 76 mini computer. Fifty frames of 20 s each were formed and summed to form a composite view. Regions of interest were defined around the kidneys and activity/time curves (renogram) formed by applying these to the original 50 frames (Fig. 1). A series of 65-s serial pictures of the kidneys were obtained during a 1000-s incremental acquisition, using a microdot imager linked to the gamma camera or, alternatively, a selected number of summed frames were displayed on grey scale statos paper. These provided visual assessment of renal and urinary tract morphology (Figs. 2 and 3). No preliminary preparation was employed and the patients were in a normal state of hydration.

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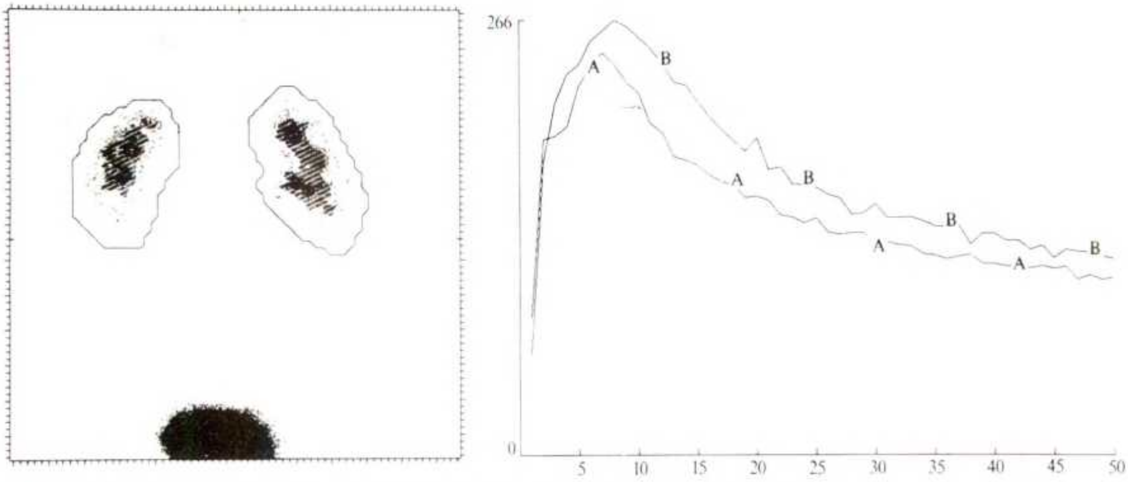


Fig. 1 Display of composite view, regions of interest and corresponding activity/time curves.

Mean Transit Time

The mean transit time of the chelate through the kidney was calculated from the deconvolution of the kidney curve with an input curve obtained by choosing a region of interest over the aorta, the normal range being 200±90 s (Diffey *et al.*, 1976).

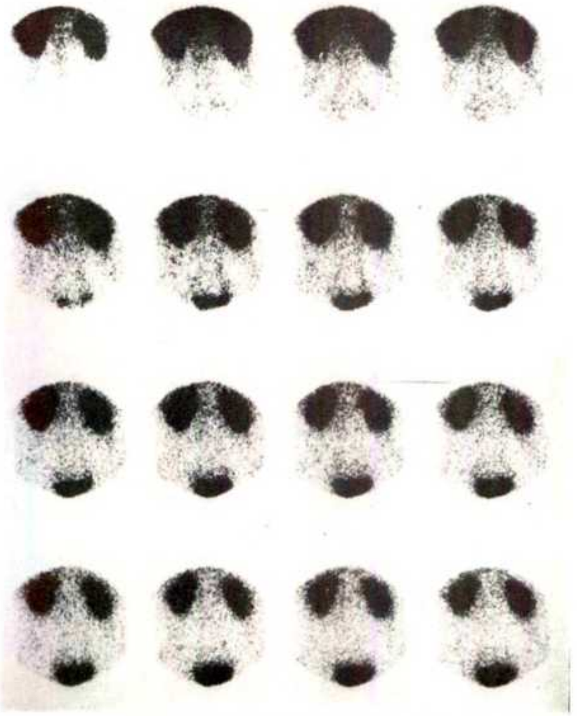


Fig. 2 Renal morphology obtained with the microdot imager linked to the gamma camera. Serial pictures of the kidneys at 65-s intervals.

Glomerular Filtration Rate (GFR)

In each case the glomerular filtration rate (GFR) was measured by external arm counting. The biological half-life ($t_{1/2}$ biol) of the chelate was the parameter used to express the clearance according to the technique described by Macleod *et al.* (1977).

Results

On the basis of the results obtained from a com-

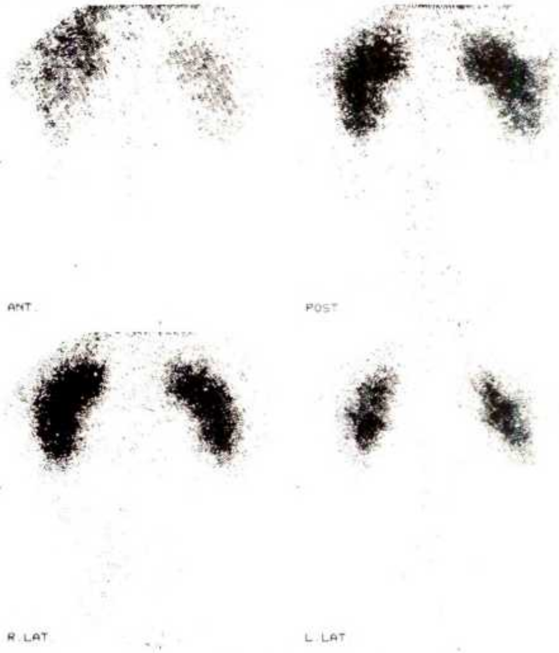


Fig. 3 A selected number of summed views displayed on grey scale statos paper.

Table 1 Group 1: 32 Patients With a Normal Excretion Urogram (IVU) and a Normal ^{99m}Tc DTPA(Sn) Gamma Camera Study. There was a Negative Correlation Between Age and the Glomerular Filtration Rate (GFR). (Correlation Coefficient r = −0.81)

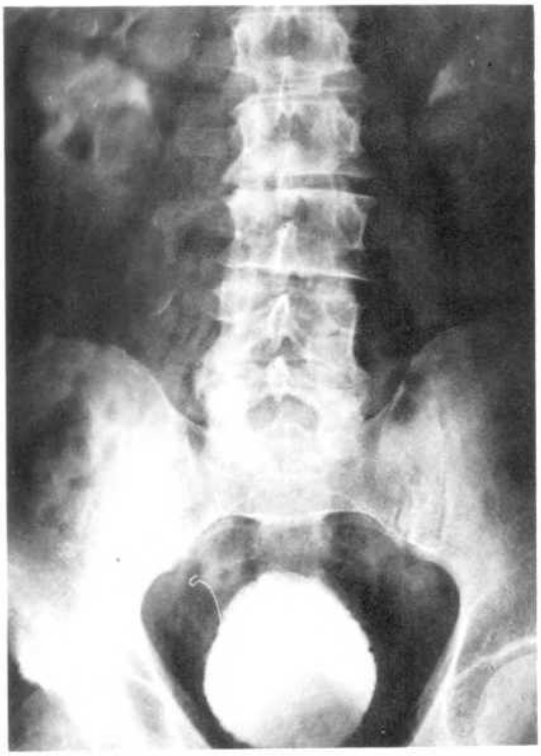
Clinical presentation	*No.*	*Mean age*	*Morphology*	*Mean MTT (seconds)*		*GFR ml/min*
				R	L	
?Outflow tract obstruction (BPH)	9	65.3 4 yr	Normal	196±55	195±50	96±24
Miscellaneous Undiagnosed loin pain (4) Cystitis Enuresis Prostatitis Perineal pain Haemospermia	23	36.2 13 yr	Normal	233±78	232±57	113±16

parative analysis of differential renal function in these patients it was possible to separate them into 3 groups.

Group 1

Group 1 consisted of 32 patients in whom both the IVU and ^{99m}Tc DTPA(Sn) findings were normal (Table 1).

Nine male patients with a mean age of 65.3±4 years presented with symptoms of outflow tract obstruction due to prostatic enlargement. The renal morphology of the ^{99m}Tc DTPA(Sn) scinti-



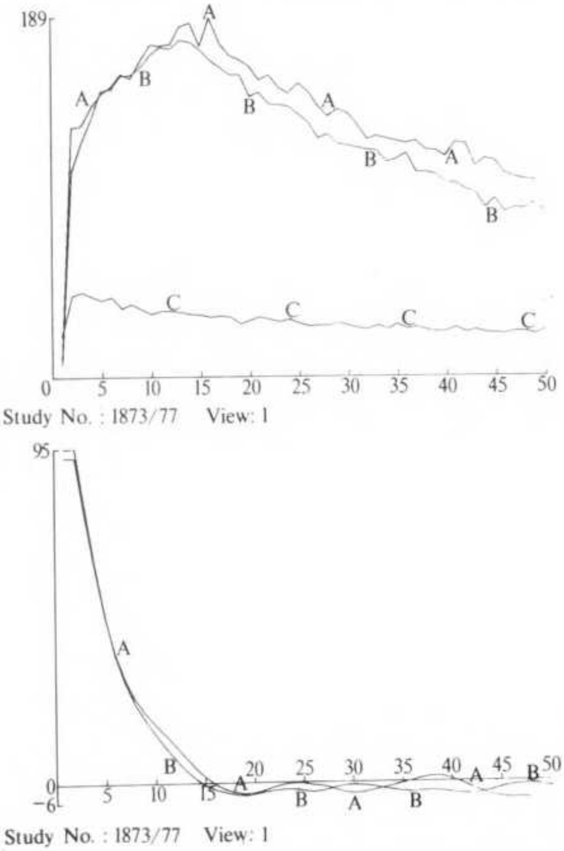


Fig. 4 (a) Excretion urogram of patient with a presumptive diagnosis of outflow tract obstruction due to benign prostatic hypertrophy showing a large post-voiding residual urine volume with normal upper urinary tracts. (b) The DTPA renogram showing a normal activity/time curve for both kidneys with good uptake and clearance of the isotope. (c) The deconvolution curve is shown intersecting the horizontal axis at the 15th frame giving a normal mean transit time of 180 s.

Table 2 Group 2: 37 Patients. Excretion Urogram (IVU) and ^{99m}Tc DTPA(Sn) Study Abnormal

Diagnosis	*No*	*Mean age (years)*	*Morphology*		*Mean MTT (seconds)*		*IVU*
			Renal	*Collecting system*	R	L	
Outflow tract obstruction BPH	6	71.6±8	Normal	Obstr.	810±252	910±231	+
Ureteric obstruction (calculus/Ca bladder)	9	41±17	Normal	Obstr.	Obstr. 992±104	Non-obstr. 239±170	+
Hydronephrosis PUJ obstruction	5		Abnormal (2)	Obstr.	804±269	293±113	+
Renal lesion	17		Abnormal			Impaired renal function	+
Cystic disease	(5)						
Trauma	(2)						
Infection							
(PN)	(4)						
(TB)	(2)						
Staghorn calculus	(2)						
Renal cell carcinoma	(2)						

BPH = benign prostatic hypertrophy, PUJ = pelviureteric junction obstruction, PN = pyelonephritis, TB = renal tuberculosis.

gram, the activity/time curves and mean transit times within the normal range indicated normal renal function (196±55 s for the right kidney and 195±50 s for the left kidney). The mean GFR in these patients was 96±24 ml/min. The intravenous urograms showed normal upper urinary tracts with no evidence of obstruction in the calices, renal pelvis or ureter. However, large volumes of residual urine were present on the post-voiding film (Figs. 4a, b and c).

Twenty-three patients with a mean age of 36.2±13 years presented with a variety of complaints; 4 presented with unexplained loin pain but no abnormality was seen on scan or emergency IVU. Mean transit times were within the normal range and the mean GFR was 113±16 ml/min. There was an inverse relationship between age and GFR (correlation co-efficient $r = -0.81$). In all of these patients the final diagnosis was made on either clinical, bacteriological, biochemical, urodynamic or endoscopic findings.

Group 2 (Table 2)

There were 37 patients in this group in whom the IVU was abnormal and the ^{99m}Tc DTPA(Sn) scintigram showed abnormal renal morphology and function. Six patients with a mean age of 71.6 years presented with outflow tract obstruction. The kidneys were normal in size and shape but there was "hold-up" of activity in the collecting system with delay in clearance of the isotope from both kidneys. The mean transit times were grossly increased with most showing no clearance for up to 1000 s or more (mean MTT, right kidney: 810±252 s, left kidney: 910±231 s). The corresponding IVU showed large residual urine volumes with dilatation of the upper urinary tracts.

Nine patients presented with ureteric obstruction visible on the excretion urogram (stone obstruction 6; carcinoma of the bladder with ureteric obstruction 2; ureterocele 1). The scintigram showed normal renal morphology but there was a hold-up of the isotope in the ureter and collecting system on the affected side; the mean transit times on the side of the obstruction were increased compared with the non-obstructed kidney (mean MTT, obstructed kidney: 992 ± 104 s, non-obstructed kidney: 239 ± 170 s). Characteristically in these patients the activity/time curve in the affected kidney showed a persistent delay in clearance of the isotope for up to several years after either operative removal or spontaneous passage of the stone as illustrated in Figures 5a, b, c and d.

There were 5 cases of hydronephrosis due to pelviureteric obstruction (PUJ). Two patients showed a non-functioning kidney on the IVU and a concomitant morphological abnormality on the ^{99m}Tc DTPA(Sn) nephrograms. A persistent impairment of renal function was noted after operative correction of the hydronephrosis as illustrated in the following case (Figs. 6a, b, c and d).

In 17 patients a renal lesion was observed on the IVU and all of these showed a morphological abnormality on the ^{99m}Tc DTPA(Sn) scintigram with varying degrees of impairment of renal function.

In patients with polycystic kidneys the scintigram showed the kidneys to be enlarged with scattered areas of non-functioning tissue corresponding to the morphological abnormality seen on the IVU. However, the renogram showed poor uptake and clearance of the isotope which also enabled a quantitative assessment of functioning residual renal tissue to be made (Figs. 7a, b and c).

Similar areas of deficiency in the uptake of the complex were also seen with tumours (Figs. 8a and b).

Group 3

The third group comprised 34 patients (Table 3)

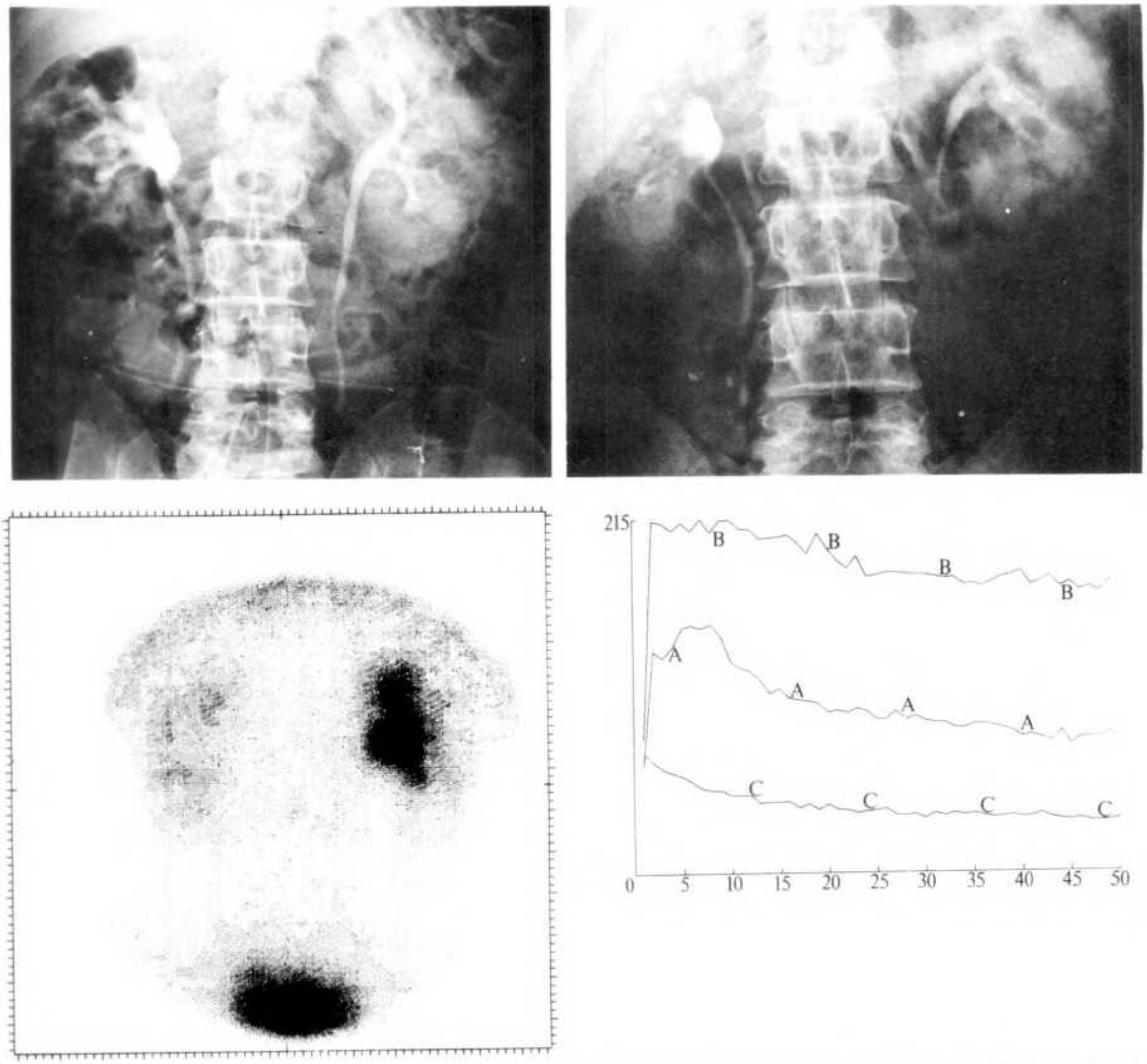


Fig. 5 (a) Excretion urogram showing a round stone in the middle third of the right ureter (opposite L3-4 vertebrae). A ureterolithotomy was performed in 1974. (b) Excretion urogram in 1977 shows a normal upper urinary tract with no evidence of stone recurrence. (c) The ^{99m}Tc DTPA(Sn) dynamic scintigram shows delay in clearance of the isotope from the collecting system in the right kidney (the right kidney is demonstrated on the right of the picture). (d) The renogram shows an abnormal activity time curve with delay in clearance on the right side.

Table 3 Group 3: 34 Patients With an Abnormal ^{99m}Tc DTPA(Sn); the Corresponding Excretion Urogram (IVU) was Either Normal or Equivocal

Clinical presentation	*No.*	*Mean age (years)*	*Morphology*		*Mean MTT (seconds)*		*IVU*
			Renal	*Collecting system*	R	L	
? Outflow tract obstruction BPH	11	65.7±9.6	Normal—10	Obstr.	360±104	444±209	PM residual Renal cyst—1
Ureteric obstruction Calculus/colic Previous operations	11	35.2±9	Normal	Obstr.	Obstr. 529±262	Non-obstr. 274±117	Normal—5 Calculus without obstruction—4 Dilated ureter—2
Undiagnosed loin pain UTI PH—renal injury	6	36.6±62	Normal	Obstr.	Obstr. 551±174	Non-obstr. 279±105	? Normal "Vascular notch"
Miscellaneous Cystitis Prostatitis Stress incontinence Ca bladder/diabetes Post-prostatectomy	6		Normal	Hold-up ureter	Obstr. 680±249	Non-obstr. 300±94	Normal Bifid pelvis Duplex

in whom the ^{99m}Tc DTPA(Sn) studies showed a morphological and/or functional abnormality, whereas the IVU was either normal or equivocal.

In this group 11 patients presented with a presumptive diagnosis of outflow tract obstruction (mean age 65.7±9.6 years). On scintigraphy the renal morphology was normal in all patients except one in whom there was a space-occupying lesion which corresponded to a renal cyst seen on the urogram. The collecting systems showed evidence of obstruction and delay in clearance of the chelate together with an abnormal activity/time curve (renogram) and the mean transit times were increased (Figs. 9a, b and c).

There were 11 patients with ureteric obstruction due to a stone or with a diagnosis of ureteric colic and 2 patients had undergone previous operations on the ureter. On scintigraphy renal morphology was normal on both sides. However, there was delay in clearance of the chelate from the obstructed kidney and the transit time was considerably increased above the normal (mean MTT 529 ± 262 s), whereas the mean transit time in the unobstructed kidney and the urinary tract was within the normal range (mean MTT, 274 ± 117 s). The IVU was normal in 5 of these patients; 2 showed dilatation of the ureter and in 4 patients a stone was present in the lower ureter without urographic evidence of obstruction (Figs. 10a, b and c).

Six patients presented with undiagnosed loin pain or lower urinary tract infection and one patient had a past history of renal injury. In all of these patients there was evidence of "hold-up" in either the calices, the ureter or renal pelvis on the scintigram and the mean transit times were markedly increased (mean MTT, obstructed kidney: 551±174 s, unobstructed kidney: 279± 105 s). The only abnormality seen on the IVU was the presence of a vascular notch either across the infundibulum of the upper calices, the pelviureteric junction or the upper ureter.

A further 6 patients had a miscellany of urological symptoms: the IVU was normal in 3, one patient had a complete duplex system and 2 patients showed evidence of a bifid collecting system. However, the scintigram showed delay in clearance with hold-up of the chelate in the calices, renal pelvis or ureter and the transit times were prolonged. This was more marked on one side than the other.

In this study there were 6 patients with false negative or false positive ^{99m}Tc DTPA(Sn) scintigrams. There were 4 patients with a false negative scan: one patient had a small paracaliceal cyst seen on IVU and 3 patients had microcalculi overlying the renal parenchyma. These lesions, being smaller than 1 cm across, were less than the resolution of the gamma camera scintigram. Two patients had false positive scintigrams due to abnormal uptake in clearance of the chelate

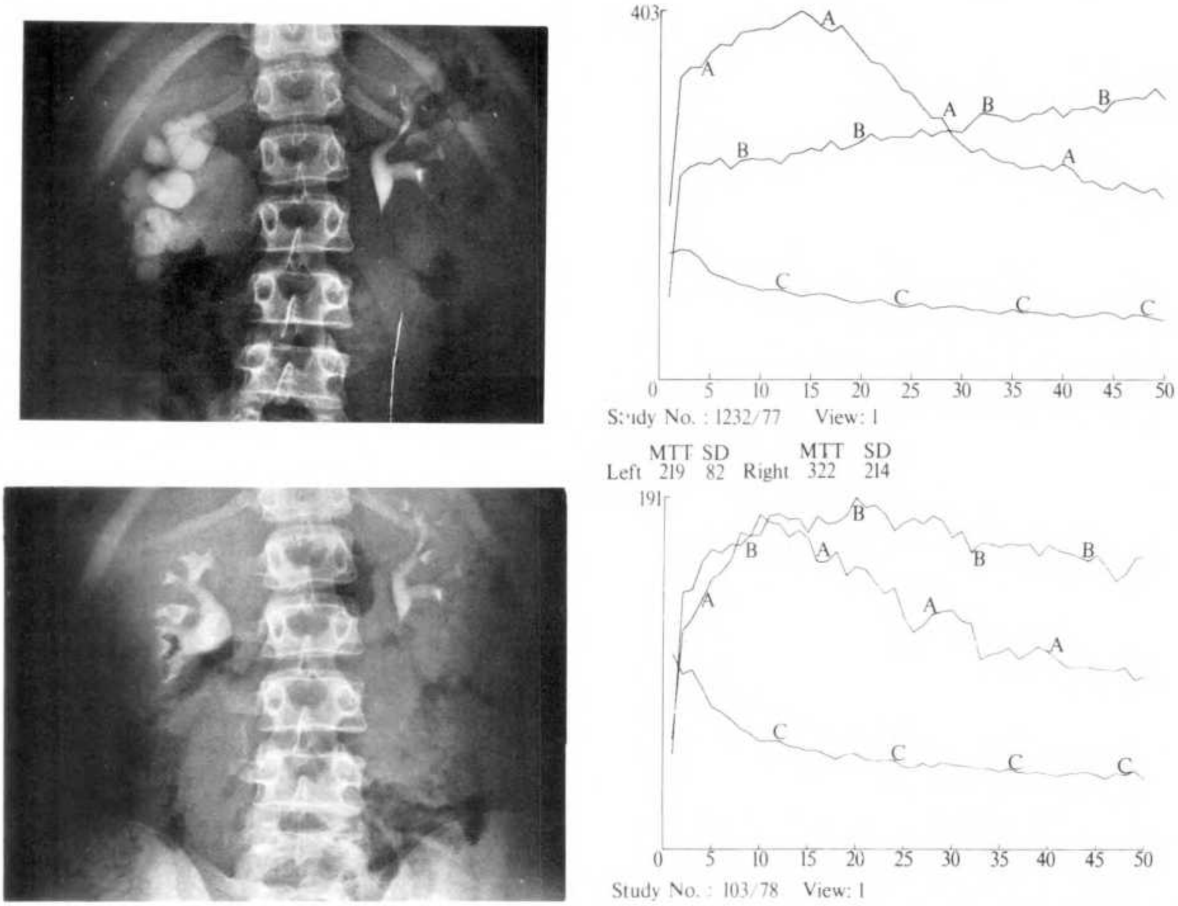
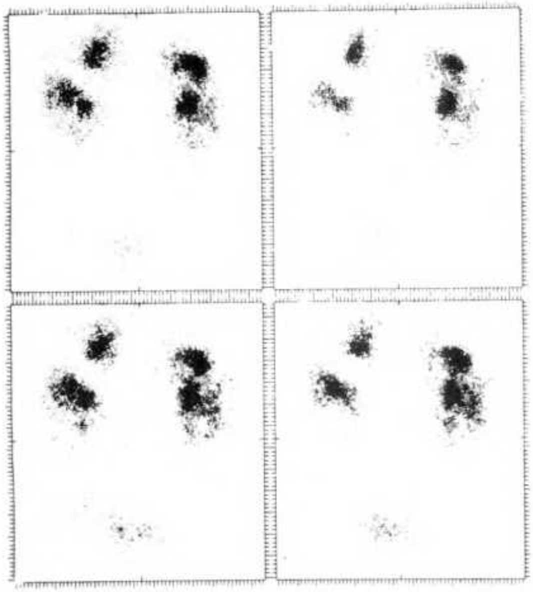


Fig. 6 (a) Excretion urogram of a 16-year-old boy with a right hydronephrosis due to pelviureteric junction obstruction. (b) The renogram shows a characteristic obstructive activity/time curve with poor uptake in the right kidney with no clearance of the isotope up to 16 min. (c) Excretion urogram following a dismembered pyeloplasty showing considerable improvement in drainage from the right kidney. (d) Renography shows improved uptake of isotope in the right kidney but there is still evidence of delay in clearance of the isotope with a mean transit time exceeding 300 s.

resulting from syncope or near syncope at the time of the examination.

Discussion

The use of the gamma scintillation camera combines renal imaging with renography and provides both anatomical and functional information (Ayre-Smith and Blake, 1976; Nielsen *et al.*, 1977; Macleod, 1978). The excellent physical characteristics of the short-lived isotope ^{99m}Tc and the renal localisation of DTPA (diethylene triamine penta-acetic acid) make this agent the radiopharmaceutical of choice for renal dynamic scintigraphy. The stannous ion forms chelates possessing a high stability constant (Mesmer and Irani, 1966; Subramanian and McAfee, 1971). This study using ^{99m}Tc DTPA(Sn) with gamma camera/computer assisted displays has shown that this chelate is superior to other popular DTPA agents. Ninety-six per cent of the injected dose of ^{99m}Tc DTPA(Sn) is cleared by the renal glomeruli compared with other technetium labelled chelates of DTPA, DMSA thioglucose and unithiol complex which are only 80% glomerular filtered (Handmaker *et al.*, 1975; Oginski and Rembelska, 1976; Macdonald *et al.*, 1977; Nielsen *et al.*, 1977; O'Reilly *et al.*, 1977). The high renal to background ratio obtained with ^{99m}Tc DTPA(Sn) gives impressive scintigraphic clarity of renal tract morphology with a dose of only 0.5 to 1 mCi and the computer processed data display morphological detail which compares favourably with the excretion urogram. An activity time curve is derived and external arm



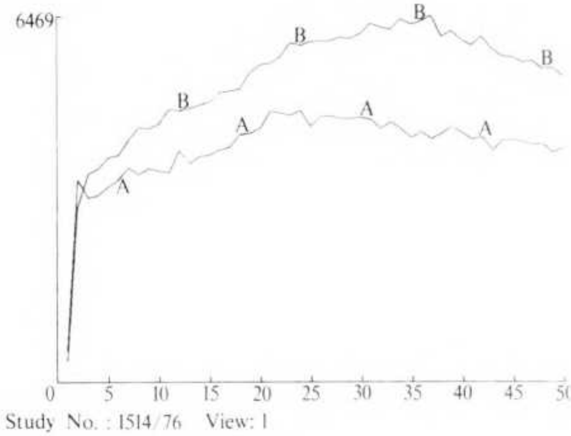


Fig. 7 (a) Polycystic kidneys: renal morphology seen on the dynamic scintigram shows scattered areas of deficient uptake of the isotope. (b) The activity/time curve shows poor uptake and clearance from both kidneys and enables a quantitative assessment of functioning renal tissue.

counting provides an accurate measurement of the glomerular filtration rate (Macleod *et al.*, 1977). Furthermore, a quantitative measurement of glomerular function can be accomplished by applying deconvolution analysis and pattern recognition to the gamma camera data (Diffey *et al.*, 1976; Houston, 1977; Macleod, 1978).

There has been valid criticism of the deconvoluted technique for measuring radio-isotope transit through the kidney which seeks to apply a rigid mathematical analysis to a physiological system that is undergoing constant change. Nevertheless, in this study the calculated mean transit time obtained by deconvolution provided a quantitative assessment of renal function which correlated with the morphological appearance of the scan, the excretion urogram and the activity time curve. Parenchymal transit times have been used to distinguish the obstructed from the non-obstructed kidney in a select group of patients (Whitfield *et al.*, 1977). More recently Houston (1977) and Macleod (1978) have shown that a

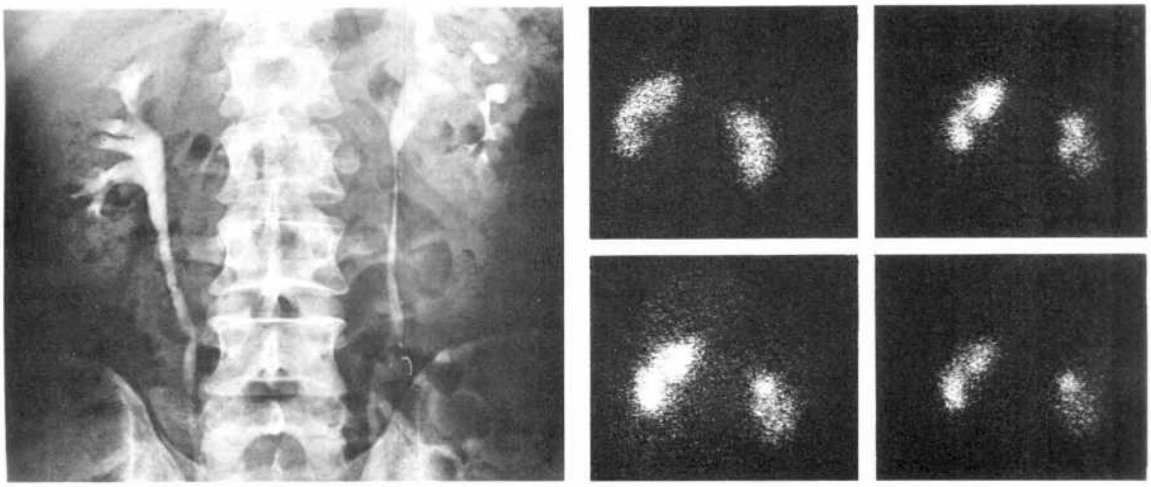
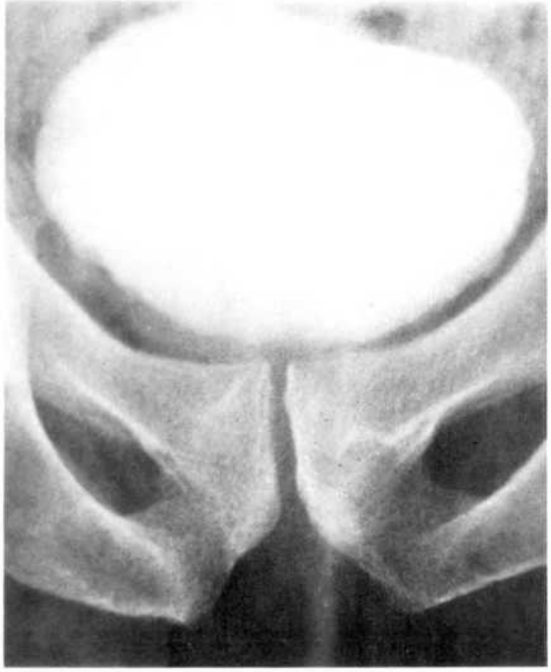
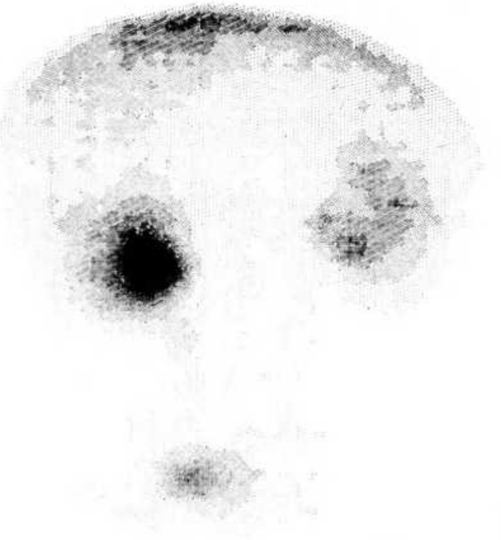


Fig. 8 (a) The excretion urogram in this 23-year-old patient with haematuria and left loin pain was reported as normal. An ultrasound examination was also reported as normal. (b) The gamma camera serial scintigram clearly shows a persistent uptake deficiency in the lower medial area of the left kidney. A selective renal angiogram confirmed tumour circulation and a timely nephrectomy was performed.





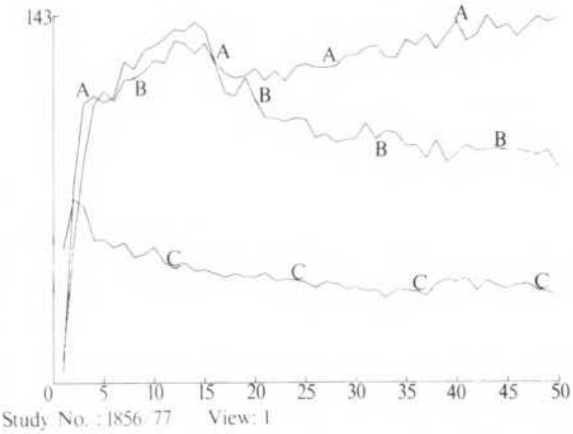
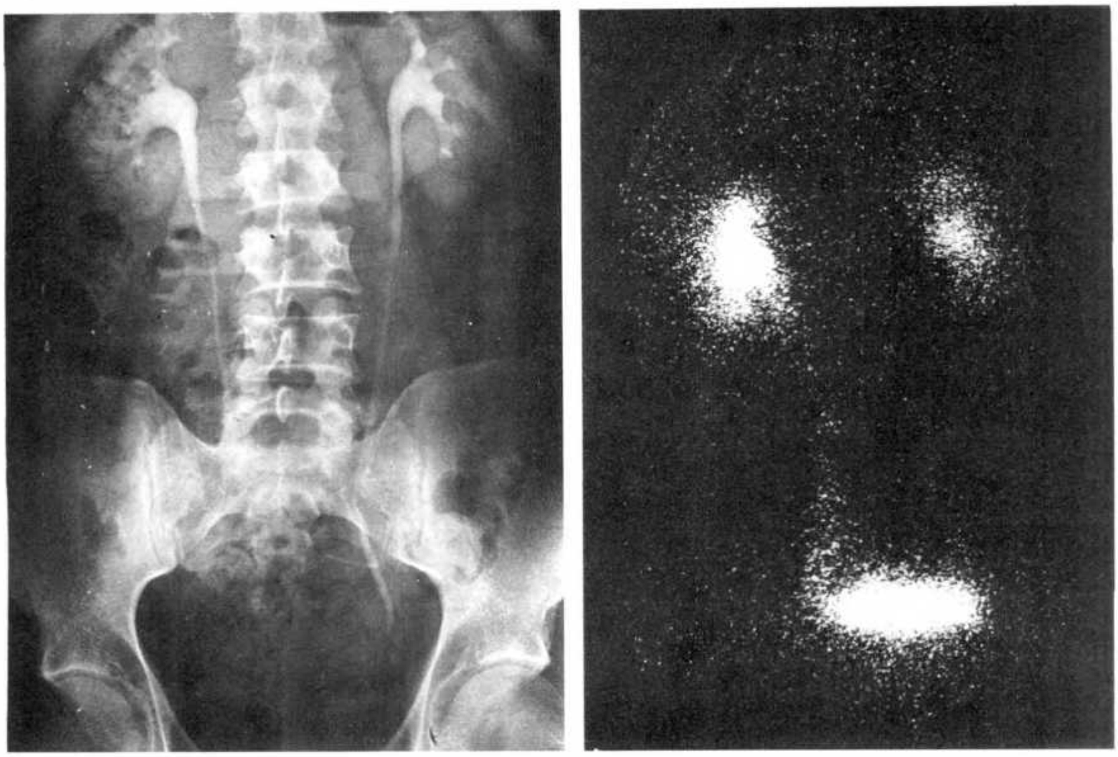


Fig. 9 (a) The post-voiding excretion cystogram of a patient with a presumptive diagnosis of outflow tract obstruction due to BPH. Note the increased residual urine volume; the upper urinary tracts were normal. (b) The gamma camera scintigram shows delay in clearance of the isotope from the collecting systems which is more marked on the left. (c) The corresponding activity/time curve (renogram) confirms delay in clearance from both kidneys which is more marked on the left than the right. Renographic evidence of impaired secretory function and delay in clearance of the isotope would appear to identify a group of patients with outflow tract obstruction potentially "at risk".

better separation between normal and abnormal renal function is obtained with the technique of feature extraction or pattern recognition using principal components, and that this technique will supplant deconvolution analysis as a means of assessing quantitative renal function (Houston, 1978).

Scintigraphy

Radionuclide renal imaging may lack the resolution and anatomical specificity provided by the urogram but it has the advantage of being a safe, non-invasive investigation for space-occupying renal lesions. Computerised isotopic section scanning and the sequential display of perfusion characteristics of renal lesions have considerably improved the diagnostic accuracy of the gamma camera scintigram in differentiating cysts from renal tumours or intrarenal vascular malformations (Black *et al.*, 1967; Tori *et al.*, 1975; Ayre-Smith and Blake, 1976; Macdonald *et al.*, 1977; O'Reilly *et al.*, 1977). In our experience the scan has been more accurate than the ultrasound examination in the detection of solid renal lesions. The gamma camera scintigram gives a pathognomonic appearance in polycystic disease of the kidneys (Joekes, 1972). Indeed, renal morphology in this condition is better visualised on the scintigram than on the nephrographic phase of the excretion urogram, while renography enables a quantitative assessment of residual functional renal tissue and provides an accurate means of monitoring the progress of the disease in these patients. The superiority of the scintigram compared with the excretion urogram in the qualitative assessment of renal ectopia, pyelonephritis



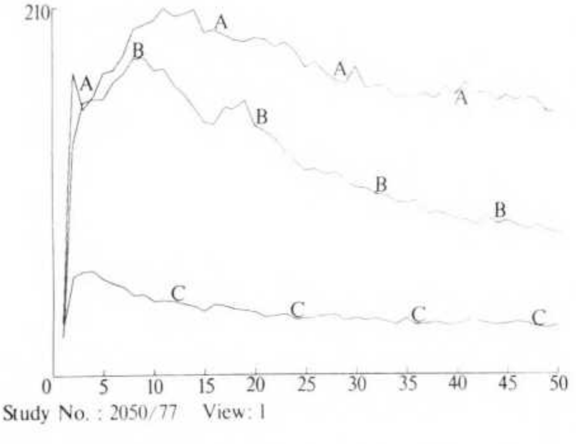


Fig. 10 (a) Excretion urogram of a patient with a small stone at the lower end of the left ureter. There is no evidence of any significant back pressure in the upper renal tract. (b) The gamma camera scintigram shows considerable delay in clearance of the isotope from the collecting system and the ureter on the left side. (c) The corresponding activity/time curve shows delay in clearance from the left kidney with a mean transit time of 300 s.

and renal trauma is well recognised (Ayre-Smith and Blake, 1976; Bueschen and Lloyd, 1976). In one of our patients with reflux pyelonephritis in the right kidney and an ectopic left kidney the excretion urogram showed an indistinct ectopic kidney but the renal scintigram clearly showed it in the left pelvis.

Glomerular Filtration Rate (GFR)

Accurate measurement of the GFR and ERPF (effective renal plasma flow) has been greatly simplified with the introduction of isotopic techniques that are reliable, easy to perform and involve minimal discomfort to the patient (Lavender, 1969; Joekes, 1972; Chisholm *et al.*, 1974; Macleod *et al.*, 1977). The technetium labelled DTPA agents which are excreted by glomerular filtration after a single intravenous dose are undoubtedly superior to 131I Hippuran which is mainly tubular secreted (90%) and requires prior localisation for accurate probe placement (Klopper *et al.*, 1972). This study confirms the inverse relationship between age and the GFR in patients without evidence of renal disease reported by Sampson *et al.* (1979). The abnormally high GFR in patients with unilateral renal obstruction is as yet unexplained and is the subject of further research. In patients with glomerulonephritis there is a greater reduction in clearance consistent with the degree of renal damage using DTPA than observed with 131H Hippuran (Meldolesi *et al.*, 1975; Macleod, 1978).

Renography

The standard 131I Hippuran probe renogram is generally regarded as a qualitative test (Joekes, 1972; Maxwell and Hayes, 1972). However, in recent years the computer derived renogram using ^{99m}Tc DTPA chelates has improved the precision and accuracy of the activity/time curve and a quantitative assessment of renal function is possible by gamma camera/computer evaluation of data and deconvolution of the renogram (Britton and Brown, 1971; Ayre-Smith and Blake, 1976; Nielsen *et al.*, 1977; O'Reilly *et al.*, 1977; Macleod, 1978). In general, no single disease, with the possible exception of acute upper urinary tract obstruction, has a diagnostic renogram associated with it and the correct interpretation of the renogram can only be made in the context of other investigations and clinical presentation (Wax and Macdonald, 1966; Joekes, 1972). Renography is certainly more sensitive to changes in renal haemodynamics and urinary drainage than the excretion urogram. It is of particular value in assessing renal function in hydronephrosis due to pelviureteric obstruction and aids in distinguishing true obstruction from an adynamic dilatation of the upper urinary tract (Otnes *et al.*, 1975; Sakurai *et al.*, 1975; Whitfield *et al.*, 1977; O'Reilly *et al.*, 1978). The success of a plastic repair for hydronephrosis can be evaluated and serial follow-up studies performed without the radiation risks associated with the excretion urogram (Wax and Macdonald, 1966; Otnes *et al.*, 1975). We have observed that the renogram following a pyeloplasty may be at variance with the IVU, showing delay in clearance of the isotope and prolonged transit times. This is explained on the basis of the renogram being tested beyond the working range of the method as far as drainage is concerned (Otnes *et al.*, 1975). Recovery of function following relief of obstruction is said to be greater when the contralateral kidney is abnormal or absent (Joekes, 1972; Otnes *et al.*, 1975).

In our patients with proven stone disease there was an abnormality in the third phase of the renogram together with delay in clearance of the isotope and prolonged transit times which persist for several years after operative removal or spontaneous passage of the stone. Less marked, but equally significant stasis was seen in patients with undiagnosed loin pain. The IVU in these patients was normal or else showed only minor variations in the anatomy of the collecting system. It is also of interest that all known stone formers and patients classified as stone formers exhibited delay in clearance on scintigraphy from either a particular group of calices or renal pelvis; in these there was no radiological evidence of obstruction, though some showed changes in anatomical configuration which hitherto have not been considered significant. This evidence of stasis therefore must be considered a possible factor in the aetiology of stone formation and in the recurrent stone former. The renogram is more sensitive than the IVU in detecting abnormalities of function when a stone is present in the ureter. It has been suggested that the basic investigation of the patient with ureterolithiasis should include an isotope renogram and a plain X-ray of the abdomen and pelvis and urography reserved for those patients in whom the renogram is markedly abnormal (Mogensen *et al.*, 1976).

An increase in the mean transit time together with an abnormal activity/time curve and delay in clearance of the isotope on the scintigram were observed in some patients with a clinical diagnosis of outflow tract obstruction, in whom the IVU showed a normal upper urinary tract. Renographic evidence of mild impairment of secretory function and delay in clearance of isotope associated with a normal excretion urogram indicates that there is a group of patients with outflow tract obstruction in whom renal function is being compromised and who are potentially "at risk". Further follow-up of these patients will indicate the importance and significance of these renographic abnormalities. Furthermore, the versatility of the gamma scintillation camera enables an accurate determination of the volume of residual urine to be made without catheterisation by measuring the radio-activity of urinary dynamics before and after voiding (Miyazaki *et al.*, 1975; Szomor *et al.*, 1976). This provides an additional technique for the objective evaluation of the patient with bladder outflow obstruction.

Renal handling of isotope is dependent upon the patient's state of hydration and the blood pressure at the time of the examination. Vasovagal hypotension associated with apprehension and low urine flow rates due to fluid deprivation may cause significant changes in renal haemodynamics resulting in an abnormal renogram

(Maxwell and Hayes, 1972; Richards *et al.*, 1977).

We now consider that the investigation of the urological patient is incomplete without the information available from a dynamic isotope scintigram.

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The Significance of Urine Leak after Pyeloplasty

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Summary—The records of 126 pyeloplasties were reviewed to discover the relationship, if any, between the duration of urine leak after surgery and the success or failure of the procedure. Half of the cases drained urine for 7 days or less. In 26 patients the urine leak lasted from 15 to 28 days: in 23 of the 26 the outcome was successful.

It is concluded that a urine leak of up to 28 days' duration is not of itself an indication for further interference. A breakdown of cases into type of operation and status of the operator (consultant or trainee) revealed no significant differences.

There is little, if any, information in the literature on the significance of urinary leakage after pyeloplasty. Some urologists deliberately vent the renal pelvis; others insist on watertight closure and recommend interference if urine leaks for more than a week. A retrospective review of 126 pyeloplasties was undertaken to see if the duration of the urinary leak after surgery was related to the outcome.

Patients and Methods

The records were reviewed of 130 consecutive pyeloplasties performed at Jervis Street Hospital between June 1961 and July 1978. The records were inadequate in 4 cases. In the remaining 126 cases, the duration of urine leakage after surgery was noted and also the apparent success or failure of the procedure.

The duration of urine leakage was taken as the number of days from operation to complete cessation of drainage.

If at review 6 months after surgery the patient was relieved of symptoms and the post-operative pyelogram seemed satisfactory, the case was recorded as an apparent success provided that there was no later evidence to the contrary. If further surgery (conservative or nephrectomy) was needed the case was recorded as a failure.

The primary operative procedures included 97 Anderson-Hynes, 21 Culp, 6 Foley operations and 2 Davis intubated ureterotomies.

Eighty-four of the operations were performed by the consultant staff and 42 by registrars in training.

Splinting with a ureterostomy *in situ* or nephrostomy was employed in 30 cases. There was no splint or intubation of the kidney or ureter in 96 cases.

The age range of the patients was from 3½ to 66 years with a mean age of 31 years.

Results

The figure shows the relationship between the duration of urine leakage and the apparent success or failure of the procedure. It can be seen that in half of the cases the urine leak was 7 days or less. In 26 cases urine leaked for between 15 and 28 days: 23 of the 26 were apparently successful.

There was no significant difference between the cases operated on by consultants and those in whom the surgery was performed by registrars in training, nor was there any significant difference in the results of the different types of operation.

Discussion

The findings in this study indicate that a urine leak up to 28 days after surgery is not of itself an indication for further interference.

The term *apparent* success became necessary when we found that of the 7 failures in the series 3 seemed successful at the time of the 6-month review but were discovered to be failures some

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Read at the 35th Annual Meeting of the British Association of Urological Surgeons in Bristol, July 1979.

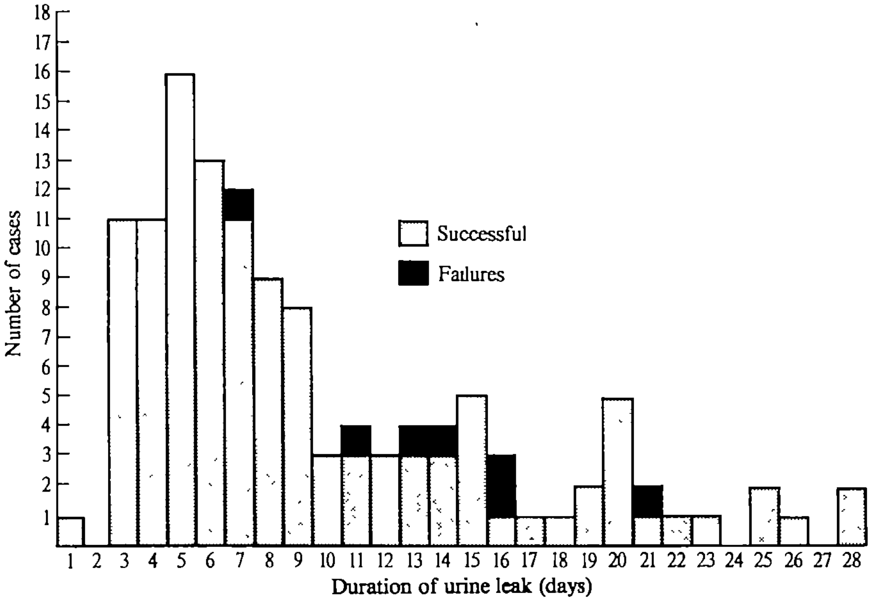

Fig. Success after pyeloplasty in relation to duration of urine leak.

years later. This suggests that there may be other failures of which we are unaware.

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Inhibition of Calcium Oxalate Crystal Growth in Urine during Treatment with Allopurinol

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Summary—Twelve male patients with urolithiasis were treated with 300 mg allopurinol daily. Urinary urate decreased from 251 ± 55 to 156 ± 19 (mean ± SD) mmol per mol creatinine. The inhibition of calcium oxalate crystal growth was measured in an *in vitro* system and the inhibition index increased from 0.51 ± 0.06 to 0.57 ± 0.08 (mean ± SD). Urinary citrate excretion was unaffected by the treatment.

Allopurinol has been successfully used in the prevention of calcium oxalate stone formation in patients with hyperuricosuria and hyperuricaemia (Smith and Boyce, 1969; Coe and Raisen, 1973; Brien and Bick, 1977; Coe, 1977; Smith, 1977). However, no convincing explanation has been presented regarding the biochemical mechanism behind this property.

Recently, we have studied the effects of allopurinol on the urinary excretion of calcium, magnesium and oxalate, but no significant changes that could explain stone prevention were observed in that group of patients (Tiselius and Larsson, 1979).

It has been proposed that urinary urate might interfere with crystallisation inhibitors (Robertson *et al.*, 1976). A decreased concentration of urate, brought about by allopurinol, would therefore favourably affect the inhibition of calcium oxalate crystallisation.

The purpose of the present study was to obtain information on the inhibition of calcium oxalate crystal growth in urine of patients with stone disease during treatment with allopurinol.

Patients and Methods

Twelve male patients with a history of recurrent calcium oxalate stone disease were treated with 300 mg allopurinol daily. During the study they kept to their normal diet and there were no special restrictions in their diet or fluid intake. The treatment was well tolerated and no further stones were observed during the first year of therapy.

Twenty-four-hour urine samples were collected from each patient before and during treatment with allopurinol. Urine was collected in bottles without any preservative. After collection the urine samples were taken immediately to the laboratory. One aliquot was frozen for future analysis of urate, citrate and inhibitory activity. Another aliquot was acidified for analysis of calcium, magnesium, oxalate and creatinine.

Analysis of calcium, magnesium, oxalate, urate and creatinine were performed by methods previously described (Tiselius *et al.*, 1978).

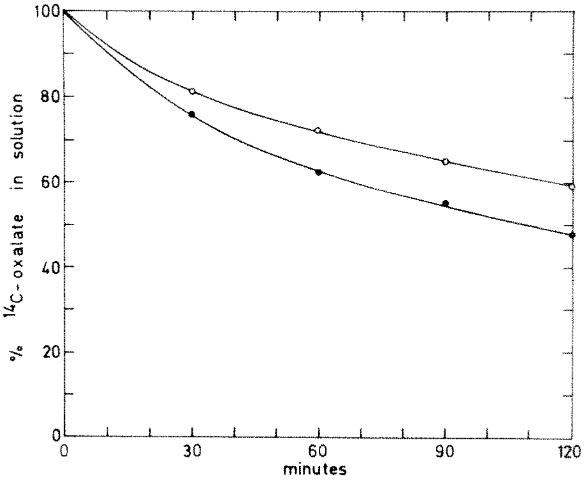

Fig. 1 Rate of calcium oxalate crystal growth in a metastable solution of calcium chloride and sodium oxalate, demonstrated as the decrease in ^{14}C-oxalate in solution at different times after the addition of seed crystals. The effect of urine (○) is compared to the effect of saline (●) and the difference between the 2 curves represents the inhibition produced by the added amount of urine.

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Citrate was determined according to Greenbaum and Pace (1970).

Calcium oxalate crystal growth inhibition was determined using a metastable system of sodium oxalate and calcium chloride at pH 6.0 (Robertson *et al.*, 1973). ^{14}C-labelled oxalate was added as a tracer. The crystallisation procedure was started by adding 2 ml of a suspension of calcium oxalate (1 mg/ml) to 50 ml of the metastable system, and the crystallisation was followed for 2 h. Crystals in the solution were removed by a Millipore filter (pore size 0.22 μm) and the isotope content was determined in 0.5 ml of the filtered solution.

The crystallisation was performed in glass bottles during continuous magnetic stirring in a water bath at a temperature of 37°C.

The urine sample to be analysed was warmed to 37°C for at least 30 min and then diluted in order to contain 5 μm of creatinine in 1 ml. The solution was filtered through a Millipore filter and 1 ml was added to the crystallisation system. The samples were run in parallel with a system containing 1 ml 0.15 M sodium chloride instead of urine.

Figure 1 demonstrates the decrease in ^{14}C-oxalate in solution at different times after addition of seed crystals with and without urine added to the system.

Samples were drawn from the solution immediately after addition of seed crystals and at 30, 60, 90 and 120 min.

Calculations

The rate constants in the system containing urine (k_i) and the system containing sodium chloride (k_c) were determined and the inhibitory index (I) expressed according to Will *et al.* (1976):

$$I = 1 - \frac{k_i}{k_c}$$

The integrated form of the crystal growth process follows the equation:

$$\frac{1}{OX_t - OX_\infty} = k \cdot t + A$$

where OX_t is the oxalate concentration in solution at time t, and OX_∞ the oxalate concentration determined by the solubility product for calcium oxalate. The conditions in this system gave the following equation:

$$\frac{1}{OX_t - 26} = k \cdot t + 0.0135$$

where t is expressed in min and OX_t is the per cent of oxalate remaining in solution at time t. The factor k is the rate constant and 0.0135 is a constant of integration.

Four values of I were recorded for each urine sample and the mean of these 4 values was used as an estimate of the inhibition index of the sample.

Results

The urinary excretion of calcium, magnesium and oxalate was not significantly altered during administration of allopurinol.

The excretion of creatinine was 15.4 ± 3.4 mmol/24 h (mean ± SD) before therapy and 15.1 ± 3.7 mmol/24 h at the time of inhibition analysis, usually 2 to 3 months after start of the prophylactic programme.

Urinary excretion of urate was decreased from 251 ± 55 to 185 ± 19 mmol per mol creatinine. This difference is statistically significant ($P < 0.01$).

The inhibition index before and during allopurinol treatment is demonstrated in Figure 2. Increased values were found in 9 patients, decreased values in 2, whereas unaffected inhibition was recorded in one patient. The inhibition index before therapy was 0.51 ± 0.06 (mean ± SD) and during therapy 0.57 ± 0.08. This difference is statistically significant ($P < 0.05$; Wilcoxon's rank sum test). In Figure 3 the combined changes in urate excretion and inhibition index are demonstrated. Although there was no correlation between the urate level and the inhibition index in this group, in most patients a decrease in urate excretion was combined with an increase in inhibition activity.

Addition of oxypurinol (gift from Wellcome Foundation, Ltd), the main metabolite of allopurinol, to the crystallisation system did not result in an altered rate of crystal growth.

The urinary excretion of citrate was 192 ± 83 mmol per mol creatinine (mean ± SD) before and 185 ± 76 mmol per mol creatinine at the time of inhibition analysis. This difference is statistically not significant. Repeated analysis of the citrate excretion during one year of treatment did not reveal any difference as compared to the pre-treatment values.

Discussion

Three different processes: nucleation, crystal

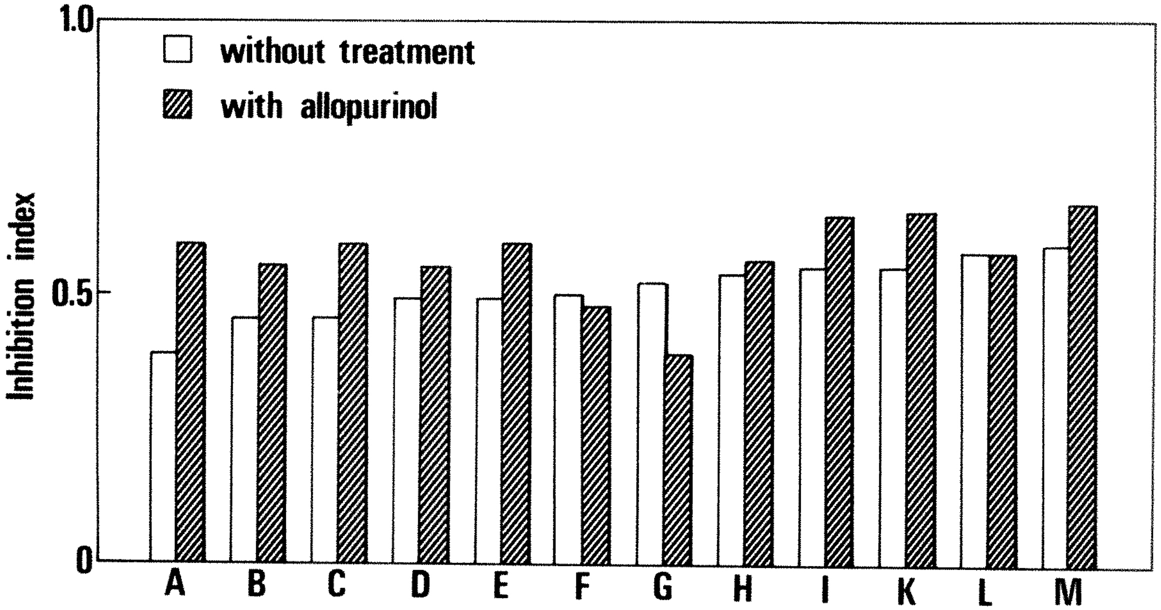

Fig. 2 Inhibition index in urine of 12 patients with calcium oxalate stone disease, before and during administration of 300 mg allopurinol daily.

growth and aggregation are considered to be important in the formation of renal stones (Fleisch, 1978). Robertson *et al.* (1976) measured the combined effect of crystal growth and aggregation and demonstrated lower levels of inhibition in patients with stone disease.

In the present study the inhibition of crystal growth was measured in an aliquot of urine containing a standardised amount of creatinine. This facilitated comparison between different patients and also comparison of the results obtained in one patient on different occasions (Tiselius *et al.*, 1978).

As is evident from Figure 1, even a very small addition of urine to the crystallisation system resulted in a significant inhibition of the crystal growth rate. Since the urine is diluted approximately 100 times, the addition of calcium and oxalate with the urine sample is insignificant and might not affect the crystallisation process.

A statistically significant increase in the inhibition of calcium oxalate crystal growth during treatment with allopurinol was observed in this group of calcium oxalate stone formers.

Several substances are known to have crystal growth inhibiting properties (Fleisch, 1978), but from the present study it is not possible to determine which substance is reponsible for the observed increase in inhibition activity.

An interaction between urinary urate and inhibiting substances, probably mucopolysaccharides, has been suggested (Robertson *et al.*, 1976) and a decreased urinary excretion of urate would result in increased levels of inhibition. The combined increase in crystal growth inhibition and decrease in urate excretion demonstrated in the present investigation give support to such a mech-

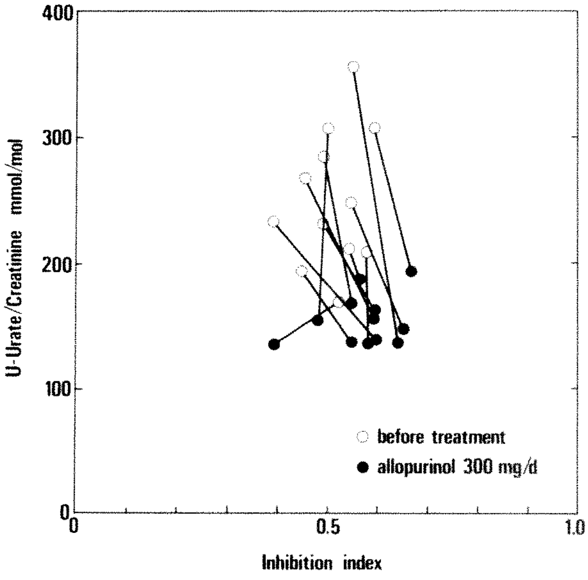

Fig. 3 Urate excretion and inhibition index in 12 patients with calcium oxalate stone disease before (○) and during (•) administration of 300 mg allopurinol daily.

anism, although it was impossible to state that there is a direct relationship between these 2 changes.

The increased crystal growth inhibition during administration of allopurinol might be of fundamental importance since it suggests that allopurinol might be of value as a prophylactic method in patients with different types of abnormalities in their urine composition. However, further studies are necessary in order to reveal the biochemical background to the observed changes in inhibition.

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Transection Denervation of the Urinary Bladder

An Experimental Study

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Summary—In an experimental study in the dog, deliberate partial denervation of the urinary bladder through partial horizontal transection achieved an alteration in detrusor activity similar to that noted in human beings following transection. It is postulated that neural escape is the mechanism responsible in the human.

Detrusor hypertonicity and hypercontractility may result from conditions such as the neuropathic bladder and the unstable bladder. The symptoms of urgency, urge incontinence and particularly nocturnal enuresis may often be distressing. Supratrigonal denervation and re-anastomosis, described for interstitial cystitis (Turner-Warwick and Ashken, 1967), were designed to denervate the upper part of the bladder and in the case described areflexia resulted, so that bladder neck resection was required to restore voiding. Later a less radical transection was described for enuresis (Yeates, 1970) and for patients with urgency and urge incontinence from various causes (Essenhigh and Yeates, 1973; Gibbon *et al.*, 1973). In these reports, although it had been thought that the operation might result in partial or total denervation of the fundus, post-operative detrusor activity showed no gross abnormality. The main benefit seemed to be due to desensitisation of the bladder, perhaps the result of damage to the intramural nerve fibres or to the muscle bundles themselves (Gibbon *et al.*, 1973).

The present study was carried out on an experimental animal to quantify the effect of neural disconnection or detrusor function. Vesical neuroanatomy was investigated, cystometry was done, and the effect of tetanic stimulation of the *Nervi erigentes* on the intravesical pressure was noted. These parameters were re-evaluated after partial horizontal supratrigonal denervation of the bladder.

Materials and Methods

Female mongrel dogs weighing between 7.5 and 14 kg were chosen. Anaesthetised dogs were catheterised and a laparotomy carried out. The neuroanatomy was studied by dissection and stimulation of the nerves by a modified peripheral nerve stimulator capable of tetanic stimulation (50/s) with a square wave of 3.75 volts dc. Cystometry was done by introducing sterile water at a rate of 5 ml/min through the catheter with a separate channel connected through a Statham transducer (P 2344) to an Atlas amplifier (EM50); values noted were plotted. This technique of peroperative 2-channel continuous cystometrography with an open abdomen was a satisfactory technique in the dogs. Voiding contractions were noted and the pressure (VP) and volume (VV) at which voiding contractions occurred were recorded. The bladder was then emptied to a volume of 50 ml and the parasympathetic nerves on both sides (successively) were subjected to tetanic stimulation; the maximum pressure (MP) thus generated, on whichever side, was also noted.

Transection was carried out on the dorsal aspect of the bladder, above the level of the ureteric orifices, extending between 2 points 1 cm lateral to each orifice. Following haemostasis, the bladder was closed in 2 layers and drained by a Foley catheter for 48 to 72 h.

After 4 weeks, the animals underwent a further laparotomy, when cystometry and nerve stimulation tests were repeated and the parameters mentioned above were recorded.

Results

Neuroanatomy (Fig.)

The canine bladder has 2 sets of nerves. The sympathetic nerve enters along the ureteric folds of the peritoneum; its stimulation has no effect on the detrusor pressure. Parasympathetic nerves

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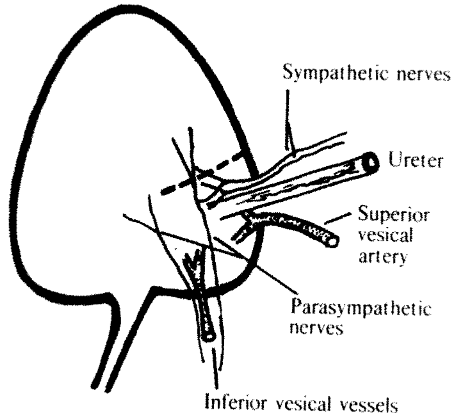

Fig. Neuroanatomy of the canine bladder seen from the side. Interrupted line indicates line of transection.

approach the bladder dorsocaudally; on each side there are 2 sets—medial and lateral, separated by a leash of caudal (inferior) vesical vessels. Horizontal transection visibly divided the medial set of nerves completely and the lateral set partially.

Cystometrography

This study was conducted on 12 dogs; values of VV, VP and MP are shown in Table 1. There was a wide range of variation, though higher values of VP occurred with higher values of VV, producing a standard slope of the cystometrogram. The maximum pressure generated by tetanic stimulation of unilateral nerves was usually higher than the spontaneously generated voiding pressure.

Transection

The supratrigonal horizontal transection technique affected approximately one-third of the circumference. Technical difficulties encountered were bleeding, proximity of the ureteric orifices to the suture line and the difficulty of maintaining post-operative catheter drainage (apart from the considerable difficulty in initial catheterisation). There were 2 post-operative deaths; the results of transection could be studied in 10 animals.

Table 1 Cystometric Results in Normal Dogs

	Range	*Mean*	*S.D.*
Volume at voiding (ml) (VV)	40-190	105.7	51.4
Pressure at voiding (cm of water) (VP)	29-80	45.6	20.8
Maximum pressure on tetanic stimulation (cm of water) (MP)	22-80	54.0	22.0

Table 2 Effects of Transection Denervation

	Pre-operative (mean)	*Post-operative (mean)*	
VV	105.7	127.5	(P 0.2-0.1)
VP	45.6	35.8	(P 0.1-0.05)
MP	54.0	4.4	($P<0.001$)

The effect of transection was a cystometric shift to the right, indicating that the voiding contractions occur at a higher volume, generating a lower voiding pressure. Measurement of residual urine could not be done because of inherent technical difficulties. In Table 2, comparison of the results shows that the alteration of VP was just significant and that of VV not significant. However, the alteration of MP was highly significant. This would indicate that despite adequate neural disconnection of the supratrigonal bladder, it was capable of generating adequate voiding contractions.

Discussion

There are difficulties inherent in applying the results of canine studies to human beings. The bladder is an intraperitoneal structure in the dog and only a partial transection, with preservation of the blood supply, can be carried out. Interpretation of results can also be difficult since the transection was made on normal bladders and it was not possible to estimate the residual urine. Despite these limitations, the similarities with clinically observed results are striking. In the reports by Essenhigh and Yeates (1973) and Gibbon *et al.* (1973) post-operative detrusor activity was essentially normal and yet clinically beneficial effects were observed. The possible explanations are the escape of some nerves, the regeneration of severed nerves or the interruption of a muscular lattice rather than neural communication (Gibbon *et al.*, 1973).

In the present study, despite incomplete denervation of the recognisable nerves, the change in bladder function was slight. Voiding occurred at a higher volume, generating a lower pressure. The contraction pattern was also essentially normal. The highly significant reduction in the maximum pressure achieved by tetanic stimulation of parasympathetic nerves, along with the voiding pattern, ruled out the possibility of regeneration of nerves or muscular disconnection being the mechanisms responsible for clinically observed beneficial effects. Thus partial denervation enables the retention of a normal voiding pattern, although this is altered. In the dog, neural escape was deliberately allowed to occur. In the human, transection is carried out from the anterior aspect and probably allows neural escape at a posterior extramural plane; this appears to be the only possible explanation for the clinically observed effects of transection of the bladder.

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The Variability of Normal Male Voiding Patterns Measured by Drop Spectrometry

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Summary—Voidings from 7 healthy men were recorded by means of the urinary drop spectrometer. The voiding patterns were characterised by the trend drop frequency and the distribution of drop time intervals.

The variability of these voiding patterns was studied by statistical techniques. The data were grouped for each person. Variances were considerable both within and between groups. Although individual differences in the mean values existed, the groups could not be separated from each other.

The method of drop spectrometry can detect voiding disturbances in an objective and consistent way (Zinner *et al.*, 1969a, 1969b, 1971; Zinner and Harding, 1971; Donkervoort *et al.*, 1975, 1977). At present we are trying to develop the method for use in screening for lower urinary tract pathology and, ultimately, for use in diagnosing particular pathological conditions.

For either purpose, the usefulness of the method depends on the ability to differentiate between individuals or between groups of individuals on the basis of the measurements. The variability inherent in any biological measurement tends to obscure the differentiation. If, however, the differences between measurements on the same individual (or individuals within the same group) are small compared to the differences between measurements on different individuals (or individuals within different groups), the measurement can be used to identify the individuals (or groups).

In this study the variability of individual normal voiding patterns, as observed by the drop spectrometer, was investigated. The results form the basis for future work on the development of diagnostic methods.

Patients and Methods

Instrumentation

The hydrodynamic instability of the external urinary stream leads to the formation of discrete drops at some distance from the meatus (Zinner *et al.*, 1969a). These drops can be observed by the urinary drop spectrometer, which has been described in detail elsewhere (Ritter *et al.*, 1976). Basically the instrument consists of a thin horizontal light sheet directed on to a photodetector (Fig. 1). When a drop passes through the light sheet, a shadow is cast upon the detector and a representative pulse appears in the output current of the detector. Information about the size, shape and spacing of the drops is contained in the pattern of the pulse sequence (Fig. 2).

Analysis of the pulse sequence can take many forms. For example, the pulse spacing, height, and shape can be analysed to extract relevant information about the mechanical and geometric properties of the urethra (Ritter *et al.*, 1977). From an instrumental standpoint, it is simplest to analyse the time relationships between the pulses, *i.e.* the pulse frequency and the distribution

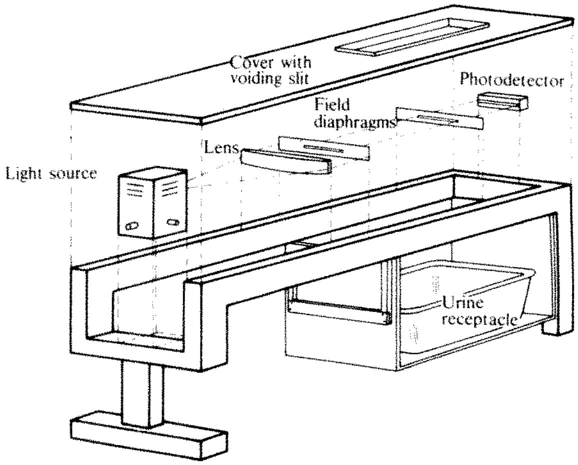

Fig. 1 Schematic drawing of the urinary drop spectrometer.

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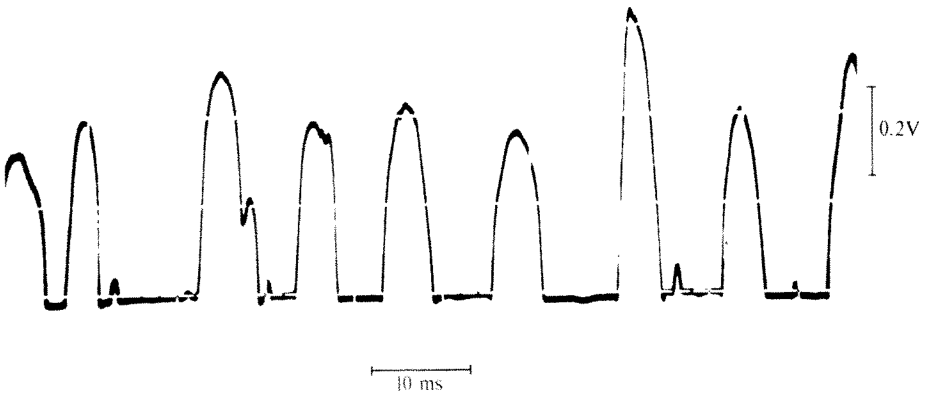
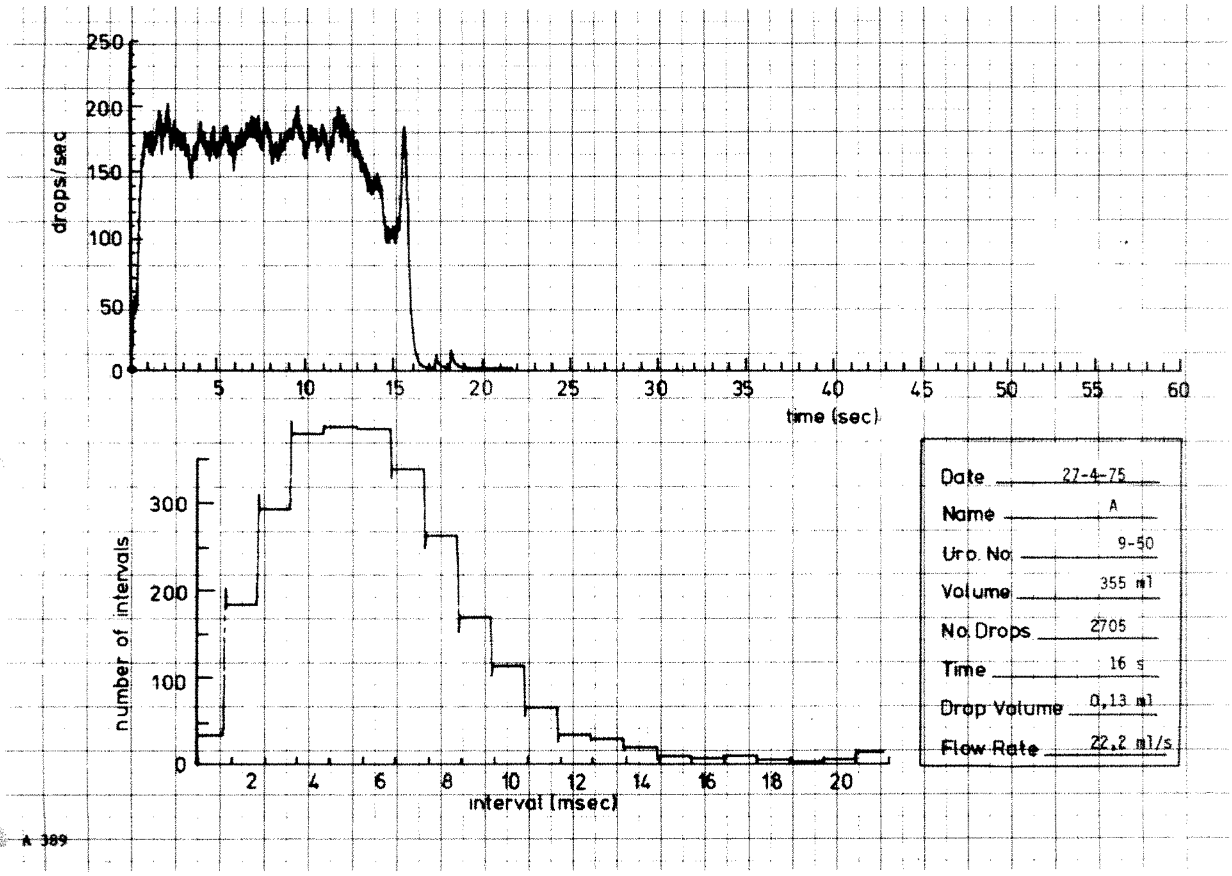


Fig. 2 Pulse train as seen on the oscilloscope.

of the time intervals between pulses. We consider only these time relationships, together with some simple averages, in this study. The details of the curves representing drop frequency and the distribution of time intervals between drops (Fig. 3), and the reduction of data from these curves for the statistical analyses are given in the Appendix.

Seven healthy volunteers (aged 24 to 44 years) with no voiding complaints and a negative routine



Date 27-4-75
Name A
Uro. No 9-50
Volume 355 ml
No. Drops 2705
Time 16 s
Drop Volume 0,13 ml
Flow Rate 22,2 ml/s

Fig. 3 Recording of a normal voiding pattern. Upper curve: trend drop frequency. Lower curve: drop time interval histogram. Box: identification data and general variables.

examination were studied; 502 voidings with volumes above 50 ml were recorded. We rejected 64 of these because of splattering stream (59) or because of hesitation or interruption during voiding (5), *i.e.* deviating patterns. Both kinds of deviation can be easily detected either during the voiding when monitoring the pulse train on an oscilloscope or afterwards by observing the recordings. In the splattering stream 2 or more drops pass through the light sheet simultaneously, giving rise to irregular pulses of high amplitudes and small intervals (Fig. 4) and a high drop frequency (Fig. 5).

The 438 non-deviating voiding patterns were characterised by 12 variables (defined in the Appendix). These variables were then used to define the variability of the normal male voiding pattern. For each individual, the mean and variance of every variable were computed. The overall mean and the variance of the means were then computed for each variable. Variance analyses were performed to check for significant differences between the individual mean values. Linear correlation coefficients between all pairs of variables were also calculated for each individual. Finally a linear discriminant analysis (Dixon, 1971) was applied to the data. The first 30 voidings from each individual were used as training data. On the basis of these data, 105 voidings (the next 15 of each volunteer) were classified in one of the 7 groups to examine the possibility of uniquely identifying individual voidings.

Results

Means and Standard Deviations

The means and standard deviations for all variables for each of the 7 volunteers are given in Table 1. The last column gives the overall means and standard deviations of the means for each variable. It can be seen that the variances of the means were of the same order of magnitude as the within-group variances.

Variance Analysis

The null hypothesis that there is no difference in the mean values for the different individuals (voiding groups A-G) was tested by variance analyses for each variable. In all cases the null hypothesis was rejected at the 99% confidence level, *i.e.* the probability that there is no difference in the means was less than 1%. A t-test was then applied to the means from paired groups for each variable. The results of these comparisons, at the 99% confidence level, are given in Table 2; a + sign indicates a significant difference between the means of a given pair for a given variable. None of the variables showed a significant difference between the means for every pair, but for the variables average drop frequency and %PEAK the difference was significant for 16 of the 21 pairs. For the variable %T67 there was a significant difference between the means of only 4 pairs. The ability to distinguish between pairs was not consistent. The pair A-B showed a dif-

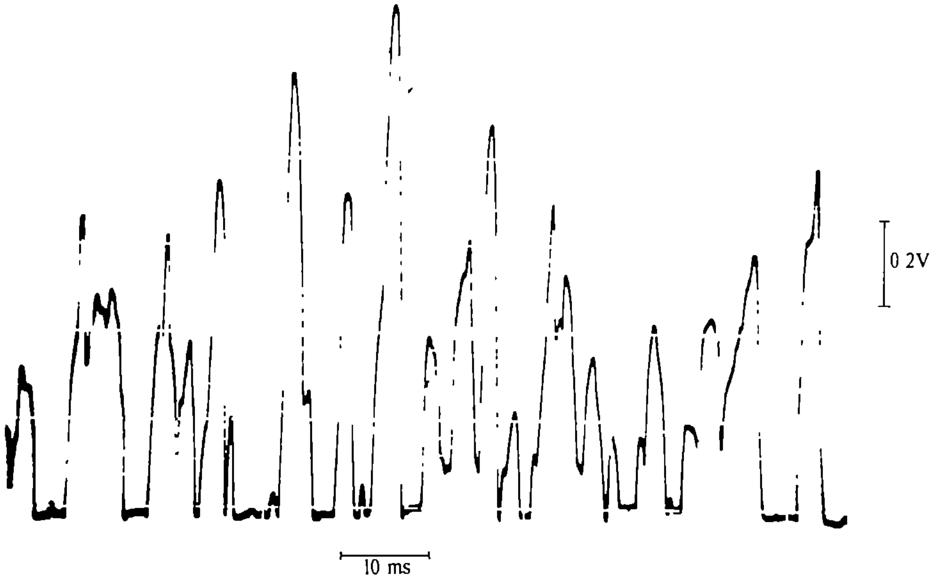
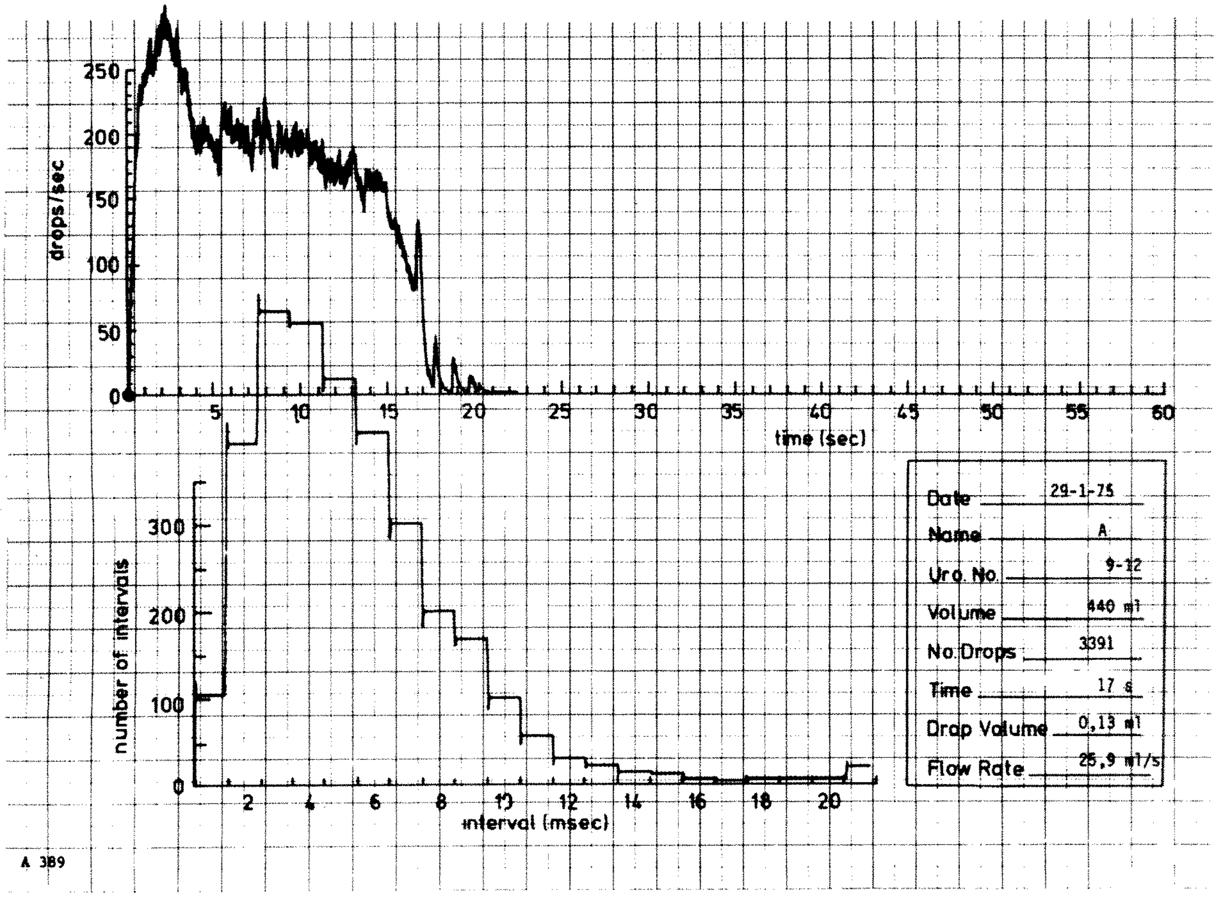


Fig. 4 Pulse train in the case of splattering.



Date 29-1-75
Name A
Uro. No. 9-12
Volume 440 ml
No. Drops 3391
Time 17 s
Drop Volume 0,13 ml
Flow Rate 25,9 ml/s

Fig. 5 Voiding pattern showing splattering at start of micturition.

ference in the means of 11 of the 12 variables but the pairs A-D and C-E differed only in one variable. Finally, the variable %T200 showed a difference only for all pairs with A, the variable %TFT for all pairs with B and the variable %T67 showed a difference for 4 subjects paired with B.

Correlations

In all 7 individuals the average flow rate was linearly dependent on voided volume for volumes less than 250 ml. For volumes greater than 250 ml, the average flow rate increased in some individuals but not in others. The details and implications of this volume dependence will be discussed in a later paper (Kramer *et al.*, 1979). Almost no correlation was found between the voided volume and the other variables.

A strong correlation existed between the average flow rate and the average drop volume in all persons (r = 0.88-0.95) (Fig. 6). The variables

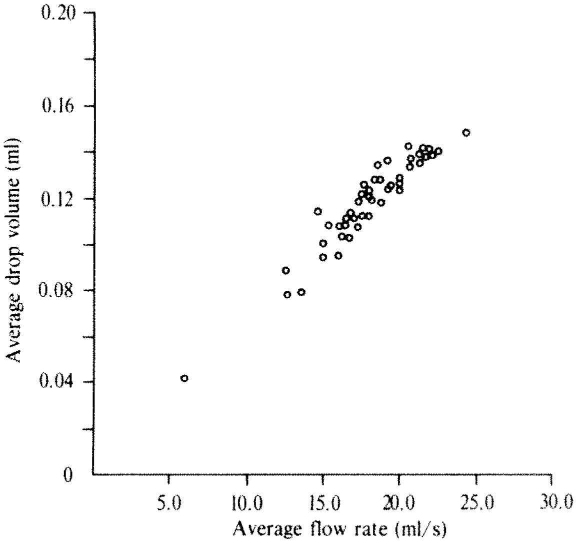


Fig. 6 Diagram of average drop volume and average flow rate for one volunteer. (Subject F, 48 voidings, r = 0.95.)

Table 1 Means and Standard Deviations of the Variables in the Different Voiding Groups. (The Variables are Defined in the Appendix)

Mean (s.d.)	*Subject* *A* *n = 57*	 *B* *n = 74*	 *C* *n = 52*	 *D* *n = 90*	 *E* *n = 47*	 *F* *n = 48*	 *G* *n = 70*	*Mean values* *N = 7*
Volume (ml)	368 (147)	217 (88)	223 (90)	423 (133)	178 (56)	261 (63)	369 (146)	291 (94)
Average flow rate (ml/s)	20.8 (4.7)	12.8 (2.0)	15.6 (4.1)	18.7 (2.4)	18.2 (3.0)	18.1 (3.2)	14.5 (2.7)	17.0 (2.8)
Average drop volume (ml)	0.124 (0.026)	0.092 (0.012)	0.113 (0.023)	0.114 (0.014)	0.136 (0.019)	0.118 (0.020)	0.114 (0.019)	0.116 (0.013)
Average drop frequency (drops/s)	167 (12.1)	140 (11.3)	137 (18.0)	164 (9.6)	133 (9.4)	153 (8.5)	126 (10.8)	146 (15.8)
%PEAK	14.9 (1.3)	11.3 (1.2)	11.9 (1.9)	14.8 (1.2)	12.8 (1.3)	13.1 (0.9)	10.8 (1.4)	12.8 (1.6)
%OVERFLOW	0.9 (0.7)	2.6 (1.3)	1.9 (1.2)	0.7 (0.6)	2.3 (0.8)	1.3 (0.8)	2.0 (1.2)	1.7 (0.7)
Peak location (ms)	5.1 (0.7)	5.8 (1.1)	6.2 (1.6)	5.7 (0.6)	6.3 (0.8)	5.8 (0.8)	7.6 (1.2)	6.1 (0.8)
%TFT	94.5 (5.5)	89.3 (8.6)	97.1 (3.9)	93.1 (4.1)	94.7 (5.1)	94.9 (6.1)	95.6 (4.8)	94.2 (2.5)
%T67	90.8 (5.7)	83.2 (8.9)	90.3 (5.4)	87.1 (5.1)	87.5 (5.8)	90.0 (8.1)	89.6 (6.6)	88.4 (2.7)
%T100	86.5 (6.8)	77.7 (8.1)	82.6 (9.6)	86.5 (5.2)	79.6 (7.3)	85.7 (8.8)	80.3 (10.2)	82.7 (3.6)
%T133	80.5 (7.5)	67.0 (9.8)	62.8 (24.3)	84.7 (6.5)	68.7 (10.9)	78.5 (7.7)	59.4 (23.1)	71.7 (9.6)
%T200	6.7 (12.4)	0.2 (1.1)	1.0 (6.9)	1.0 (3.3)	0.0 (0.0)	0.9 (4.3)	0.0 (0.0)	1.4 (2.4)

Table 2 Significant Differences between Mean Values ($\alpha = 0.01$). (The Variables are Defined in the Appendix)

Voiding groups	*Volume*	*Average flow rate*	*Average drop volume*	*Average drop frequency*	*%PEAK*	*%OVER-FLOW*	*Peak location*	*%TFT*	*%T67*	*%T100*	*%T133*	*%T200*	*Total*
A-B	+	+	+	+	+	+		+	+	+	+	+	11
A-C	+	+		+	+	+	+				+	+	8
A-D												+	1
A-E	+	+		+	+	+	+			+	+	+	9
A-F	+	+		+	+							+	5
A-G		+		+	+	+	+			+	+	+	8
B-C		+	+					+	+				4
B-D	+	+	+	+	+	+		+		+	+		9
B-E		+	+		+			+					4
B-F		+	+	+	+	+		+	+	+	+		9
B-G	+		+	+			+	+	+				6
C-D	+	+		+	+	+					+		6
C-E			+										1
C-F				+	+						+		3
C-G	+			+	+		+						4
D-E	+		+	+	+	+				+	+		7
D-F	+			+	+								3
D-G		+		+	+	+	+			+	+		7
E-F			+	+		+							3
E-G	+	+	+		+		+						5
F-G	+	+		+	+	+	+				+		7
21 pairs	12	13	10	16	16	11	8	6	4	7	11	6	

representing the percentages of flow time with more than 67, 100 and 133 drops per second were also correlated to each other. All other variables, however, proved to be quite independent as judged from their linear correlation coefficients.

Discriminant Analysis

The discriminant analysis uses statistical methods to find the differences between groups of data in a multidimensional space, one dimension for each variable. If only 3 variables are used, the procedure can be visualised as follows. When the data are plotted in 3-dimensional space, a "cloud" is formed for each individual group. The more compact the clouds and the greater the distance between them, the easier it is to distinguish between the groups of data. Conversely, if the data form a diffuse fog rather than individual clouds, the groups cannot be distinguished. The extension to multidimensional space can not be visualised, but the procedure is mathematically the same. The analysis first uses training data to form the clouds and then looks at the test data. For each test datum, it calculates the probability that it belongs to a particular cloud.

In this study there were 7 individuals, *i.e.* 7 groups of data. For the classification of the training data, only 47 of the 210 voidings (22%) were assigned to the correct individual with a probability greater than 75%. This indicates that the groups of data are not well defined and appear rather foggy in the multidimensional space. For the classification of the test data only 14 of the 105 voidings (13%) were assigned to the correct group with a probability greater than 75%.

Discussion

In this paper we have described the properties of normal voiding patterns as characterised by the spectrometer method, a method still in the experimental stage. In this study all voided volumes over 50 ml were usable for analysis. This represents an advantage over the usual flow meter performance for which it is generally accepted that voided volumes under 100 ml invalidate the result and should be ignored (Shoukry *et al.*, 1975).

The sensitivity of the spectrometer method (Ritter *et al.*, 1974) was demonstrated by the number of individual differences found in the mean values of the variables (Tables 1 and 2). The variables used here were also found to be mostly mutually independent. However, no acceptable group separation could be obtained by the discriminant analyses. This implies a considerable overlap of the data in the different voiding groups, as can also be seen in Table 1. The variance analysis indicates that the data from the different individuals can not be treated as coming from the same population for the calculation of overall means and variances. So the total variability can not simply be reduced by increasing the number of voidings. The standard error of the overall mean ($s_{\bar{x}}$) can be taken as a measure for this variability. It is computed from the variance within the groups (s^2_w), the number of voidings in each group (n), the variance of the means (s^2_b) and the number of groups (N) as:

$$s_{\bar{x}} = \sqrt{\frac{\frac{s^2_w}{n} + s^2_b}{N}}$$

From the values of the respective within-group and between-group variances taken from Table 1, it follows that the variability does not change appreciably if more than 4 voidings per person are considered.

It is concluded that because of its sensitivity to changes in the drop pattern, the method of drop spectrometry seems suited for computerised screening procedures to detect early pathological changes in the lower urinary tract. However, this study of 7 normal men indicates that the ranges of the reference values for normals will be quite large. It may therefore be more rewarding to conduct longitudinal studies where each individual furnishes his own reference values and individual regressions with age can be observed.

It might be expected that differences in voiding patterns between individuals taken from groups with outflow tract problems will be greater than those between the 7 normal men described in this paper. The clinical discrimination problem will then be less difficult to solve. Thus the sensitivity of the method to voiding differences, as we have shown here, indicates that the easier clinical application is possible.

Acknowledgement

The authors gratefully acknowledge the assistance of Dr J. Hermans, Department of Medical Statistics, University of Leiden, in the statistical analyses.

Appendix

Registration and Data Reduction

The registration of each voiding consisted of (Fig. 3):

1. The trend drop frequency curve.
2. The distribution of time intervals between the drops.
3. Some general data.

The distribution of time intervals was registered as a 0 to 20 ms histogram with 1 ms classes. All intervals exceeding 20 ms were collected in the 21st or overflow class.

The voiding patterns were characterised by 12 variables. General variables were computed from the voided volume, the total flow time and the total number of drops in the voiding. The voided volume was measured in a graduated cylinder. The total flow time (TFT) was defined as the time during which the drop frequency was above the level of 17 drops per second (Fig. 7).

Four general variables were used in this study: the voided volume, the average flow rate (volume/TFT), the average drop volume (volume/number of drops) and the average drop frequency (number of drops/TFT).

From the time interval histogram, 3 variables were defined: the class number of the histogram peak (peak location) and the percentages of intervals in the peak (%PEAK) and in the overflow bin (%OVERFLOW) (Fig. 7).

The drop frequency curve was characterised by the percentages of the total voiding time (Fig. 7) during which the drop frequency was above levels of 17, 67, 100, 133 and 200 drops per second. These percentages were called %TFT, %T67, %T100, %T133 and %T200 respectively (Fig. 7).

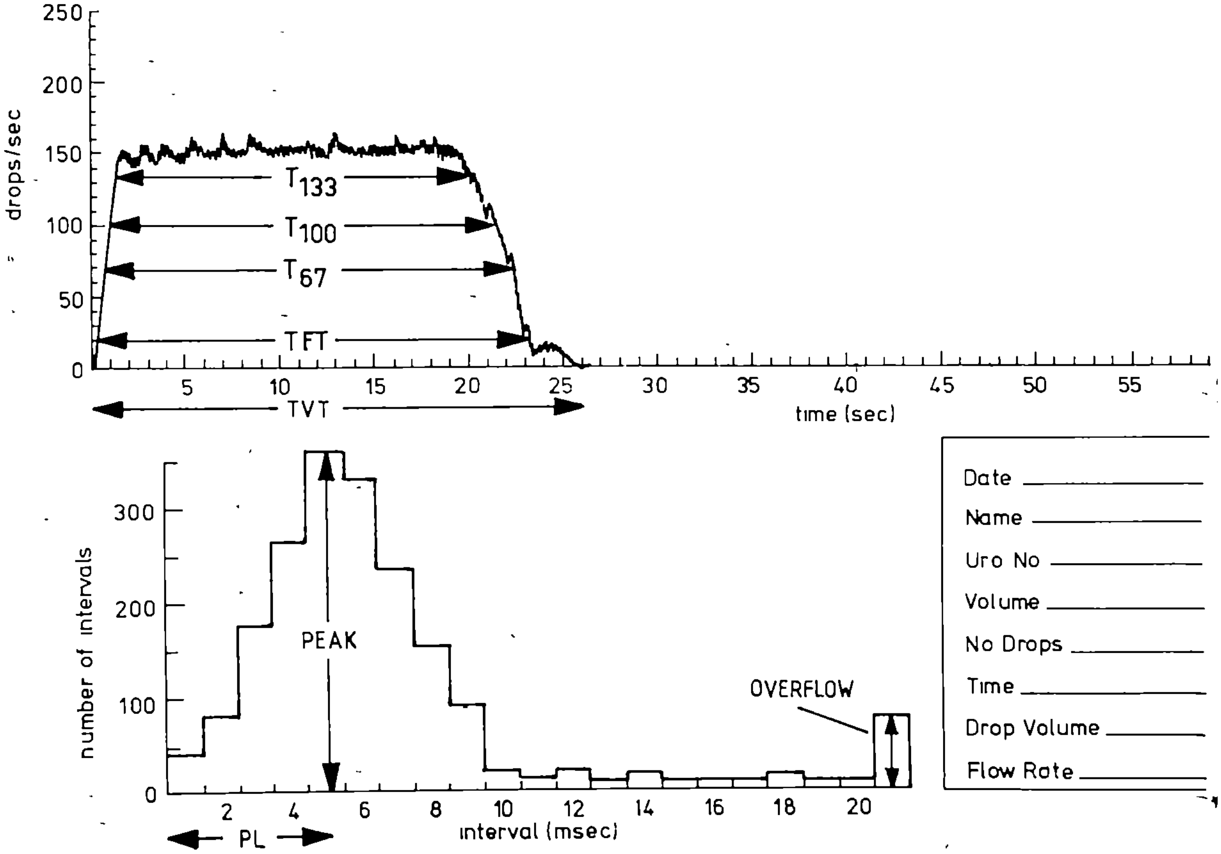


Fig. 7 Illustration of the variables obtained from the curves. TFT: total flow time. TVT: total voiding time. PL: peak location.

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Evaluation of the Role of Injection Therapy for Benign Prostatic Hypertrophy

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Summary—Intraprostatic phenol injection treatment was given to 13 cases of benign prostatic hypertrophy (BPH) without urinary retention. Symptomatic improvement was significant, although objective assessment showed neither significant alteration in the size of the prostate nor in the urinary flow rate.

Injection therapy is considered inadequate in the relief of prostatic obstruction.

Various non-operative forms of treatment for benign prostatic hypertrophy have evolved over the years, *e.g.* hormones (Gingell *et al.*, 1972; Bourke *et al.*, 1974; Farrar and Pryor, 1976), cryotherapy (Soanes and Gonder, 1966) and phenol injection (Talwar and Pande, 1966), none being effective enough to replace surgical extirpation. Injection therapy has been tried by other workers (Shipman and Akile, 1967; Angell, 1969; Smith, 1969), the results being judged by symptomatic improvement and the restoration of voiding ability. However, spontaneous restoration of ability to void following a period of catheter drainage is not uncommon and symptoms may improve following even placebo treatment (Castro and Griffiths, 1971).

Phenol injection therapy is based on the concept of chemical necrosis of the prostatic tissue and consequent sloughing or shrinkage of obstructive elements of the tissue. The present study was undertaken to assess both subjective and objective measurements and thus to evaluate the effectiveness of injection therapy.

Materials and Methods

Thirteen patients with BPH causing significant symptoms were selected for the study on the basis of the following criteria:

1. Palpably enlarged and clinically benign prostate.
2. Absence of acute or chronic retention.
3. Reluctance to undergo surgery.
4. Ability to void at least 150 ml of urine per act (for uroflowmetry).

Pre-injection evaluation consisted of (i) assessment of symptoms, (ii) estimation of prostatic size, (iii) excretion urography including cystography and planimetry, (iv) uroflowmetry and (v) estimation of residual urine. Following a course of injections, a similar evaluation was made. Four patients were eventually operated upon and in-

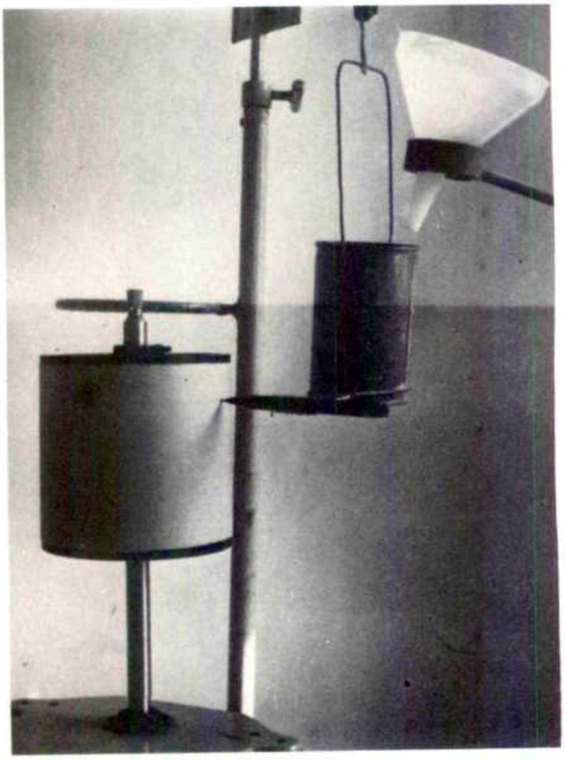

Fig. 1 A simple uroflowmeter.

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jected prostatic tissue was therefore available for histopathological study.

Bimanual examination was done with the patient in the supine position with the legs drawn up and the bladder empty; independent assessment was made by the 2 authors and the "mean estimated value" in grams was recorded.

A gravimetric uroflowmeter recording continuously on a rotating drum was devised (Maulik, 1976). From the maximum slope of the curve of descent the maximum flow rate (MFR) in ml/s was computed. This device, tested on normal healthy volunteers, was found to be capable of accurate reproduction (Fig. 1).

Voided volumes above 150 ml only were accepted. The mean value of 2 successive voidings was recorded.

Cystographic planimetry gave 2-dimensional measurements of the size of the bladder and the prostate (Aubrey and Khosla, 1971; Abrams *et al.*, 1976). Results of planimetry showed a wide discrepancy from the actual measurement of residual urine and hence was discarded. The measurement of prostatic size (Thuman, 1951) was also rejected in favour of measurement of the height of the prostate in relation to a fixed point on the symphysis pubis (Vermooten and Schweinsberg, 1964).

The injection technique, as described by Talwar and Pande (1966), was immediately preceded by catheterisation (enabling estimation of residual urine) and an assessment of the size of the prostate. The amount injected was, however, double the standard amount—5 ml per injection more or less evenly distributed in the 2 lobes. The injection was repeated after one week and sometimes at further weekly intervals; on average 3 or 4 injections per subject were carried out. Post-injection evaluation was done 2 weeks after the last injection. In a preliminary study, prostatography with water-soluble dye using the same injection technique had confirmed that the correct plane (between the capsule and the adenoma) was reached.

Table 1 Effect of Injection Treatment on Symptomatology

Symptoms	*No. of cases*	*Improved*	*Unaltered*	*Deteriorated*
Frequency	13	11	1	1
Urgency	5	5	—	—
Hesitancy	11	10	—	1
Poor stream	5	5		
Incomplete evacuation	10	8	1	1
Need to strain	9	7	1	1

Table 2 Objective Assessment Following Injection Treatment (Mean Values)

	Pre-injection	*Post-injection*
Digitally estimated size	31 g	21 g
Radiological "height"	1.88 cm	2.70 cm
Maximal flow rate (ml/s)	10.9±4.5 (s.d.)	12.3±7.6 (s.d.)
	(P 0.5-0.4)	
Residual urine (ml)	125.4±38.4 (s.d.)	87.1±43.8 (s.d.)
	(P<0.01)	

Results

The mean age of the patients was 68 years (range 55 to 90 years) and the mean duration of symptoms 31 months (range 3 months to 20 years).

All of the clinical symptoms showed significant improvement, to the extent of 86.8% overall improvement (Table 1).

The results of the objective assessment are shown in Table 2. The *estimated size* of the prostate shrank following injection; contrary to this,

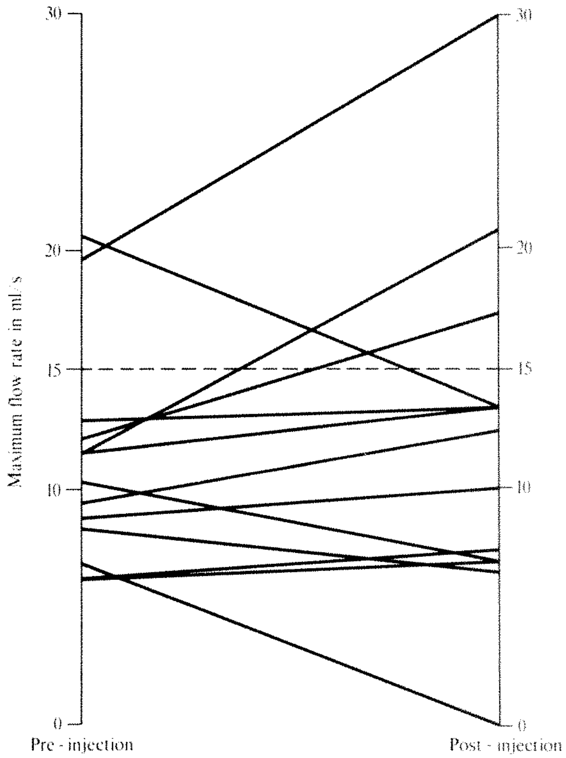

Fig. 2 Changes in the MFR following injection therapy.

radiological measurement of the "height" of the prostate from the mid-point of the symphysis pubis showed an increase.

The MFR showed no significant difference (*P* 0.5-0.4) between the pre-injection and post-injection values. A minimal normal MFR of only 15 ml/s (Sandoe *et al.*, 1959) was present in only 2 cases before and 3 cases after injection therapy. Both pre-injection and post-injection mean values were subnormal (Fig. 2).

Residual urine was estimated by catheterisation in each patient once immediately before and once after injection therapy. The differences shown were significant ($t = 6.27$ and *P* 0.01).

Histopathological examination of the previously injected prostate after an interval of 10 days to 6 months was possible in 4 patients. The most consistent feature was focal necrosis (Fig. 3), though the largest was only 1.5 cm in diameter. Other notable features were round cell infiltration, vascular thrombosis (one case) and fibroblastic proliferation (one late case).

Discussion

The simplicity of injection therapy, if effective, would offer an attractive alternative to surgery. Reports in the literature suggesting that it is effective have been based on observations such as digital estimation of the size, volume of residual urine and restoration of the ability to void following retention, which do not stand scientific scrutiny. Neither the mechanism of retention nor that of its spontaneous relief is known; hence restoration of voiding can only be an unreliable guide. The efficacy of any non-operative treatment can only be judged by its effect on the size of the prostate and more so on the cross-sectional area of the urethra.

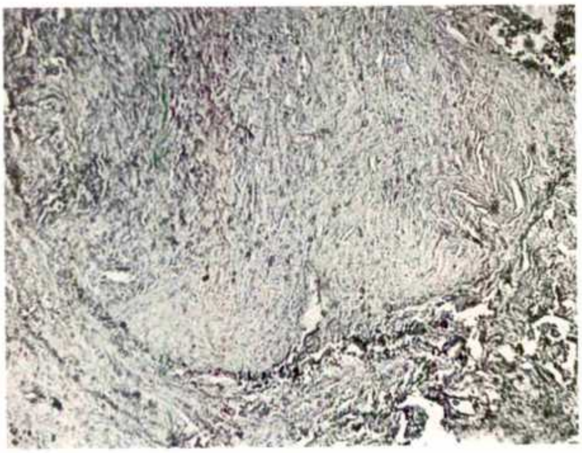

Fig. 3 Focal necrosis of the prostatic tissue following injection.

Non-retained cases only were selected in the present study. There was marked symptomatic improvement, similar to that produced by hormones (Gingell *et al.*, 1972) or placebo (Castro and Griffiths, 1971).

Digital estimation of the size of the prostate is the least reliable objective measurement (Bissada *et al.*, 1976). Previous workers have laid stress on this measurement and our study was able to confirm that although digitally the prostate appeared to be smaller, radiologically there was an actual increase in size. Both digital and radiological estimates are liable to be inaccurate (Vermooten and Schweinsberg, 1964).

Despite the inherent risks, catheterisation was performed for the actual measurement of residual urine because planimetry was found to be unreliable. Although there was a significant reduction in the volume of residual urine following injection, single estimates could be misleading. Moreover, the relationship between residual urine value and the degree of prostatic obstruction is not established (Castro and Griffiths, 1972; Abrams *et al.*, 1976). On the contrary, the relationship between the MFR and the cross-sectional calibre of the urethra is well established (Lenaghan, 1970; Castro and Griffiths, 1972). In this study, injection failed to show significant improvement in the MFR and a "normal" flow rate was restored in only one case. On the other hand, acute retention was precipitated in one case following injection.

Even with a higher than standard dosage, microscopically only minimal focal necrosis was distinguishable; other changes were minimal. Necrosis and infarction leading to fibrosis and shrinkage are among the possible effects of injection; sloughing of prostatic tissue is probably the result of inadvertent vascular injury. In this study, although one case of vascular thrombosis was noted, there was no sloughing as reported previously.

Thus it seems that injection therapy is an inadequate form of treatment of BPH. It fails to have any significant effect on either the size of the prostate or the urinary flow. There is, however, qualitative improvement in symptomatology, reduction in the digitally estimated size of the gland, reduction in residual urine and some degree of focal tissue necrosis. Overall effectiveness of injection therapy remains inconsequential.

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Treatment of Advanced Prostatic Cancer with Parenteral Cyproterone Acetate: A Phase III Randomised Trial*

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Summary—Forty-two patients with previously untreated T3/4 N1-4 M0/1 prostatic adenocarcinoma were treated with either cyproterone acetate (n = 21; 300 mg intramuscularly per week) or oestradiol undecylate (n = 21; 1·00 mg intramuscularly per month) after extensive staging which included open skeletal biopsy and pelvic lymphadenectomy in some cases. Subjective and objective parameters as well as signs of drug toxicity were recorded regularly.

Evaluation after 6 months showed cyproterone acetate to be more effective in the following respects: (1) the significantly different castration effect as judged by plasma testosterone, (2) the objective voiding pattern and tumour response, with regression of palpable and histologically evaluable local tumour in 16 of 21 patients, and (3) side effects and untoward reactions.

Thus cyproterone acetate is suggested as a valuable alternative in the treatment of advanced prostatic cancer.

Curative treatment of prostatic carcinoma is hampered primarily by the following factors. Firstly, 70 to 90% of all carcinomas extend beyond the organ boundary at the time of diagnosis (T3/4 N1-4 M1) and are therefore not suitable for radical surgery. Secondly, the primary response to conventional regimens such as orchiectomy and oestrogen administration depends on the grade of tumour differentiation, leading to primary failure or secondary relapse. Thirdly, "what oestrogen treatment wins from the cancer, it more than loses to other causes of death". This pessimistic statement by the Veterans Administration Cooperative Urological Research Group (1967) on the high rate of cardiovascular side effects of oestrogens stimulated the search for new forms of treatment in prostatic carcinoma patients. This has included such alternatives as synthetic, less toxic oestrogens, progestogens, antiandrogens, antiprolactins, inhibitors of adrenal steroidogenesis, cytotoxic agents and irradiation.

Cyproterone acetate is a synthetic ^{21}carbonsteroid with low oestrogenic, androgenic or corticoid activity but with pronounced progestational and antiandrogenic potencies (Bridge and Scott, 1964; Neumann and Kramer, 1964; Neumann and Elger, 1966). On a peripheral level, cyproterone acetate rapidly suppresses plasma testosterone (Schoonees *et al.*, 1971; Morse *et al.*, 1973; Brotherton and Barnard, 1974) owing to impaired testicular Leydig cell function (Hoffmann and Breuer, 1968; Markewitz *et al.*, 1969). Moreover, studies from our laboratory have indicated that the metabolic clearance rate of testosterone is increased and the biological half-life shortened after cyproterone acetate administration, resulting in a decreased production rate and a medical castration effect (Hutschenreiter *et al.*, 1977).

At a prostatic, intracellular level, cyproterone acetate inhibits cytosolic dihydrotestosterone binding (Geller *et al.*, 1975) and the formation of a nuclear chromatin-dihydrotestosterone-receptor complex (Walsh and Korenman, 1971) without reduction of cytoplasmic androgen uptake and turnover (Walsh and Korenman, 1971; Hutschenreiter *et al.*, 1977). These effects of cyproterone acetate as an androgen antagonist justify its classification as an antiandrogen.

We have studied 42 patients with inoperable prostatic adenocarcinoma in a randomised phase III comparative study. Patients were treated with either oestradiol undecylate†, a conventional oestrogen, or with cyproterone acetate‡, an antiandrogenic drug.

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* Preliminary results of a joint study.

† Progynon Depot^{R}, Schering AG, Berlin.

‡ Androcur^{R}, Schering AG, Berlin.

Patients and Methods

Forty-two patients entered the trial over a period of 15 months. Criteria for entry required that all patients had histologically proven adenocarcinoma, including classification of tumour grade (GO-GIII), had not been treated previously, and had either T3 or T4 N1-4 M0/1 lesions (UICC, 1978).

Criteria for exclusion were cardiovascular or hepatic disease, urinary obstruction requiring catheter drainage and a life expectancy of less than 6 months. The age range was 51 to 84 years (average 67.6 years).

Clinical tumour stage was assessed by rectal examination, cystoscopy, intravenous urography with roentgenographic proof of residual urine, chest X-ray, bone survey, radioisotope scan, serum phosphatases determination (total acid, prostatic, alkaline; conventional method), open skeletal diagnosis by random iliac crest puncture including bone marrow exfoliative cytology and acid as well as prostatic phosphatase determination and additional bone histology.

All patients had had pedal lymphangiography and 5 patients also had a staging pelvic lymphadenectomy.

Morphological studies were based on at least 2 transrectal needle biopsies (Tru-Cut Needle) examined by the same pathologist from the German Prostate Cancer Registry. All patients had additional prostatic cytology studies (Franzén Needle) of at least 4 cytology slides, examined and cross-checked by 2 cytologists independently.

The criteria for the full clinical examination and follow-up evaluation are given in Table 1. Differentiation between the specific criteria of the performance status, indexed 0 to 100, was carried out as suggested by Karnofsky (1953). Patients were questioned and examined for drug toxicity and side effects, gynaecomastia, cardiovascular and thromboembolic changes or water retention at monthly intervals. In the oestrogen group (monthly injections), plasma was sampled after 3 and 6 months' treatment, *i.e.* 4 weeks after the third and sixth injection. In the antiandrogen group (weekly injections), plasma was sampled after 3 and 6 months' treatment, *i.e.* 1 week after the twelfth and twenty-fourth injection.

Design of the Trial

Cyproterone acetate (300 mg/week intramuscularly) or oestradiol undecylate (100 mg/month intramuscularly) was randomly allocated to 2 groups of 21 patients each. Since it was felt that in advanced disease short-term treatment would allow a valid comparison, the study was limited to 6 months. Treatment was stopped if, at any time, tumour progression required other forms of treatment, or cardiovascular or hepatic side effects occurred and necessitated such a change (Fig. 1). After the 6-month evaluation, all patients entered into our previously reported therapy protocol (Kurth *et al.*, 1977) according to the presence or absence of distant metastases.

Table 1 Follow-up Protocol

	BEGIN			MONTHS			END
		1	2	3	4	5	6
Subjective *General:* performance state, weight, pain, analgesics	●	●	●	●	●	●	●
Urological: frequency, nocturia, stream, rectal examination	●	●	●	●	●	●	●
Objective IVU, residual urine, uroflowmetry, histology, cytology, chest X-ray, bone survey, bone scan	●						●
	Lymphangiography Lymphadenectomy skeletal biopsy						
Laboratory Blood count, ESR, liver and renal tests, phosphatases, clotting analysis, urine analysis, plasma testosterone	●			●			●

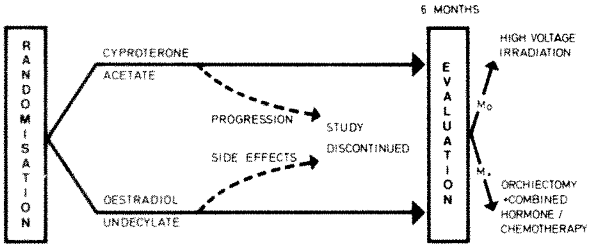

Fig. 1 Protocol of phase III trial of cyproterone acetate (i.m. 300 mg/week) versus oestradiol undecylate (i.m. 100 mg/month) over 6 months. After the final evaluation, patients entered our previously reported protocol (Kurth *et al.*, 1977).

Oestradiol undecylate was chosen because it is a long-acting oestrogen: a dose of 100 mg of this oestrogen is equivalent to 80 mg of polyoestradiolphosphate (Estradurin) and both of these applications are considered "low-dose" oestrogens.

Results

Pre-treatment Status The patients in the 2 groups were of comparable age (average 67.3 versus 67.8 years) and of similar tumour stage and grade (Table 2). In each group there were 18 patients with obstructive and irritative symptoms and impaired uroflow studies; 2 patients in each group had painful metastases.

Abnormal urograms with residual urine and/or upper tract dilatation were present in 9 patients in the antiandrogen group and 8 patients in the oestrogen group. The frequency of infected urine or elevated serum acid phosphatase was approximately similar in both groups.

Effect of Treatment

There was a more pronounced ($P<0.05$) suppression of testosterone during oestrogen treatment than with cyproterone acetate treatment after 6 months (Fig. 2). In the cyproterone acetate group, plasma testosterone dropped from an initial 434 ± 42.7 SEM to 107 ± 14.2 SEM ng/100 ml after 3 months and remained at this level after 6 months (102 ± 16.6 ng/100 ml).

Table 2 Correlation of Tumour Stage (UICC) and Grade of Differentiation (GO-III)

Groups	*Stage T3/4*		*Grade*	
	M0	*M1*	*GO-I*	*GII-III*
Cyproterone acetate	15	6	13	8
Oestradiol undecylate	14	7	13	8

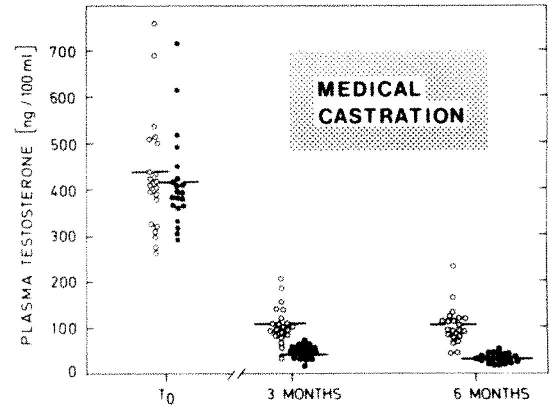

Fig. 2 Effect of cyproterone acetate (•; n = 21) and oestradiol undecylate (○; n = 21) on plasma testosterone before (T0) and after 3 and 6 months' treatment. The hormone was determined by duplicate double-antibody solid phase radioimmunoassay (Biolab-Zinser, Frankfurt, Germany).

Oestradiol undecylate however, resulted in a fall of testosterone from 416 ± 51.1 to 38 ± 4.1 after 3 months and to 29.6 ± 3.7 ng/100 ml after 6 months of treatment (Fig. 2).

The clinical responses were as follows:

Performance Status The patients with metastatic bone pain in both groups responded promptly to treatment, but one oestrogen-treated patient relapsed after 4 months, requiring analgesics again. Of the oestrogen-treated patients, 19 gained weight (0.5 to 3.5 kg), whereas only 12 patients in the cyproterone group did so. Assuming a Karnofsky Index above 60 to be acceptable (Karnofsky, 1953), no significant difference in the 2 forms of treatment was observed. However, general well-being was markedly influenced by the frequency of side effects seen after oestrogen treatment (see below).

Micturition Of 21 patients on oestrogens, 14 noted improved voiding symptoms (hesitancy, dribbling, force of stream, nocturia, frequency) and a similar number of patients did so after cyproterone acetate treatment. Objectively, however, cyproterone acetate resulted in an improved voiding pattern (maximal flow rate, voiding time) in 15 patients, whereas this was true for only 9 individuals treated with oestrogen (Fig. 3).

Tumour Response Table 3 indicates the rates of objective response. Rectal examination was always done by the same investigator and recorded at weekly intervals; this was the only information on tumour size, as ultrasonography or computer-

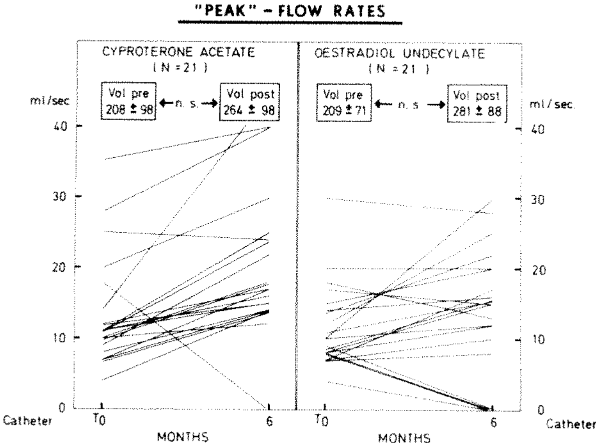

Fig. 3 Peak flow rates before (T0) and 6 months after cyproterone acetate or oestradiol undecylate treatment. Voided volumes did not differ significantly (Student's t-test). One patient in the cyproterone acetate group and 4 patients in the oestradiol group developed urinary retention, requiring a catheter; 15 patients in the cyproterone acetate group and 9 patients in the oestradiol group had peak flow rates above 15 ml/s after treatment.

ised tomography was not used routinely. Sixteen of 21 patients under cyproterone acetate treatment showed regression of palpable and histologically evaluable local tumour. In 11 patients the prostate was reduced to a soft, flat area which was even difficult to biopsy. In 9 of these patients no remaining tumour could be identified 6 months after therapy, although sufficient prostatic tissue was available for histology (Fig. 4). Conversely, 2 patients in the oestrogen group showed objective tumour progression with enlargement of osseous or new development of soft tissue metastases after 6 months. One cyproterone acetate-treated patient with stable M1 disease had marked local tumour progression with deterioration of the upper urinary tract and total bladder outlet obstruction shortly before the end of the trial. None of the patients in either group ceased treatment as a result of tumour progression and there was no tumour-related death.

Table 3 Objective Response after Cyproterone Acetate and Oestradiol Undecylate Treatment

Criteria	*Cyproterone acetate (n = 21)*	*Oestradiol undecylate (n = 21)*
Local tumour mass		
regressed	16 (11 T0)	11 (2 T0)
stable	2	8
progressed	3	2
Histological regression but tumour still present	10	11
No tumour upon re-biopsy (T3/4 → P0)	9	2
Decreased acid phosphatase	13	15
Improved urogram	5	1
Improved bone scan	1	0

Toxicity and Side Effects Two patients treated with oestrogen died 7 and 12 weeks after initiation of treatment due to myocardial infarction or pulmonary embolism. One patient in this group was withdrawn from the study after 3 months because of severe thrombosis of the right leg. While there were virtually no untoward reactions after cyproterone acetate treatment, except for diminished libido with impotence, there were many side effects in the oestrogen group and, in 2 patients, transient deterioration of liver function (Table 4).

Discussion

The aim of this trial was to determine whether cyproterone acetate was superior to a conventional intramuscular oestrogen preparation in terms of tumour response and drug toxicity. Special attention was given to the clinical, pathological and biochemical evaluation and the monitoring of side effects.

The interpretation of previous studies using cyproterone acetate for prostatic cancer has been limited by several factors. Firstly, by the oral administration of the drug, as the intestinal reabsorption of cyproterone acetate is incomplete unless administered in non-encapsulated form (Speck *et al.*, 1976); in addition, the effectiveness of oral administration depends upon the reliability of the patient. Secondly, by the inconsistent and therefore non-comparable evaluation of tumour stage in previous studies. Thirdly, by the fact that

Table 4 Toxicity and Side Effects after Cyproterone Acetate and Oestradiol Undecylate Treatment of 42 Patients

Toxicity	*Cyproterone acetate (n = 21)*	*Oestradiol undecylate (n = 21)*
Death	—	2
Gynaecomastia	2 (mild)	21
Oedema, thrombophlebitis	—	8
Lower extremity thrombosis	—	1
Coronary heart disease	—	5
Gastrointestinal symptoms	1	4
Pathological liver tests	—	2
Pruritus, dermatitis	—	3
Impotence	19	21

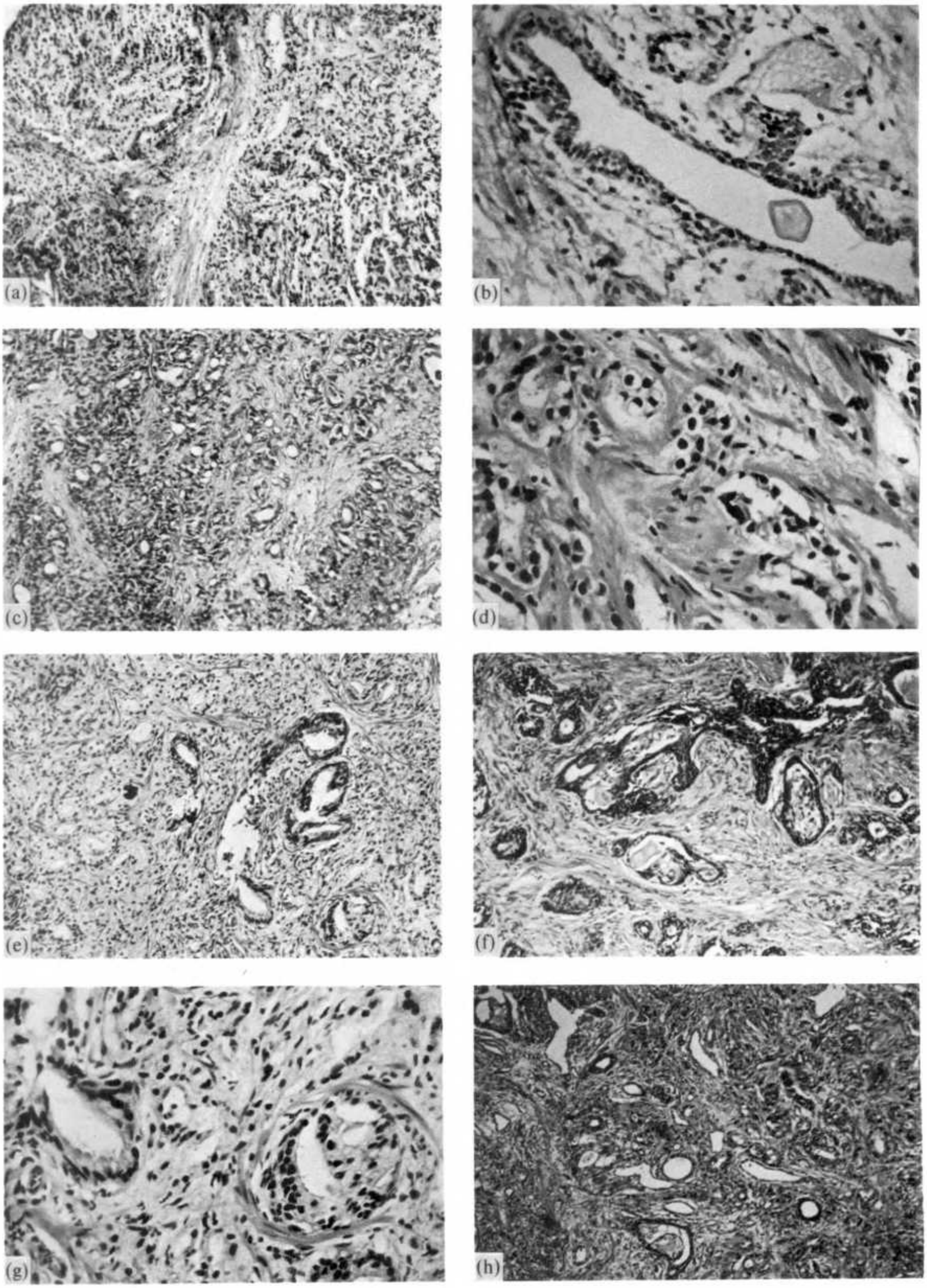
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)

Table 5 Benefits of Oral Cyproterone Acetate (200-300 mg/day). (n = 474)

Author	*After unsuccessful treatment*		*Previously untreated*	
	Patients (n)	*Response*	*Patients (n)*	*Response*
Scott and Schirmer (1966)	—	—	10	5/10 phosphatase 7/10 tumour mass 5/10 pain relief
Geller *et al.* (1967)	—	—	2	all with objective remission
Geller *et al.* (1968)	5	?	5	4-14 months
Nagamatsu (1971)	10	temporary subjective	12	?
Veneema (1971)	—	—	39	2 months given, generally pain relief 15/16 phosphatase
Mauermayer (1971)	66	7/7 stage D stable 20/60 w/o response	—	—
Mellin (1971)	*13*	3/13 (all patients dead after 14 months)	*7*	5/7 at least stable
Smith *et al.* (1973)	35	19/28 overall	—	—
Wein and Murphy (1973)	*22*	9/20 prostate size 3/6 phosphatase 6/13 pain relief 2/7 micturition overall?	*26*	16/25 9/12 7/11 6/12 overall?
Bracci (1978)	222	?	—	—
Total number	373 patients previously treated		101 patients previously untreated	

most patients treated previously had received other forms of antiandrogen therapy and developed secondary unresponsiveness. Fourthly, by the lack of controls under randomised conditions.

On the other hand, we believe that placebo controlled trials in patients with advanced cancer present ethical problems.

Our study has several features in common with the EORTC protocol (EORTC Urological Group, 1977). The predictive value of the EORTC study, however, might be adversely influenced by the fact that cyproterone acetate was administered orally and that previous prostatectomy and surgery for the relief of lower urinary tract obstruction during the trial were accepted additional regimens.

Our results on testosterone suppression are in keeping with those observed by Sciarra *et al.* (1971) after diethylstilboestrol and cyproterone acetate.

In reviewing the literature, no study fulfilling phase III criteria was available for comparison. Table 5 is a compilation of all reported cases of orally administered cyproterone acetate, although in several studies information on tumour remission is incomplete. Those patients reported repeatedly by the same author have been listed only once.

Of the 474 patients included in Table 5, 373 had received cyproterone acetate following various forms of surgical and medical antiandrogen treatment (orchiectomy, oestrogens, antiandrogens) and 101 were previously untreated. In the group of previously treated patients, reports from Smith *et al.* (1973) and Wein and Murphy (1973) give the most valid information on tumour response. The former authors found an overall objective

Fig. 4 (*a*) Cribriform and solid carcinoma of the prostate prior to cyproterone acetate treatment. (*b*) Atrophic glandular and stromal structures without carcinoma 6 months after cyproterone acetate (P0); rectal palpation = T0. (*c*) Solid anaplastic and poorly differentiated adenocarcinoma of the prostate prior to cyproterone acetate treatment. (*d*) Carcinoma with pronounced regression seen as shrunken nuclei, vacuolised cytoplasm and stromal reaction 6 months after cyproterone acetate treatment. (*e*) Pluriform prostatic carcinoma with glandular, poorly differentiated, cribriform and solid elements prior to oestrogen treatment. (*f*) Prostatic atrophy with squamous metaplasia and absent carcinoma 6 months after oestrogen treatment; rectal palpation = T0. (*g*) Cribriform and solid carcinoma prior to oestrogen treatment. (*h*) Carcinoma still present admixed with atrophy and metaplasia (moderate regression). Staining was performed using haematoxiline-eosine with standard technique. Magnifications are (a) ×25; (b) ×160; (c) ×25; (d) ×160; (e) ×25; (f) ×25; (g) ×160; (h) ×25.

and subjective response in 19 of 28 patients, while the latter investigators noted decreased tumour size in 9 of 20 and relief of bone pain in 6 of 13 individuals.

In the group of untreated prostatic carcinoma patients, the parameters best documented by Scott and Schirmer (1966) and Wein and Murphy (1973) are the decline of serum acid phosphatase in 14 of 22 patients, reduced local tumour mass in 23 of 35 and relief of bone pain in 12 of 21 patients. Geller *et al.* (1968) noted an objective remission lasting from 4 to 14 months in all 5 previously untreated patients with T3/4 M0/1 lesions.

The only data on intramuscular administration of cyproterone acetate for treatment of prostatic cancer were compiled by Klosterhalfen *et al.* (1973) and Burchardt and Agrapidakis (1972), who reported on the same study. As these authors treated 42 patients in a prospective study first orally and afterwards intramuscularly, these data are not included in Table 5. Klosterhalfen *et al.* (1973) reported a markedly lower tumour-related and non-tumour-related death rate after cyproterone acetate as compared with oestrogen-treated controls.

In comparing the tumour response in the 2 groups in our study, 2 features are of paramount interest: the favourable regression of clinically and histologically determined local tumour mass and the virtually negligible side effects after cyproterone acetate treatment. The lack of drug toxicity is in agreement with previously reported results (Geller *et al.*, 1968; Smith *et al.*, 1973; Wein and Murphy, 1973; Denís and Declercq, 1978). As reported by Burchardt and Agrapidakis (1972), no hepatic or renal damage was detectable after more than 3 years of treatment.

With regard to objective and subjective parameters, cyproterone acetate was clearly superior to oestrogen (Table 3), although the castration effect was more pronounced after oestradiol undecylate (Fig. 2). Oestradiol undecylate resulted in a high frequency of untoward reactions (Table 4), including a cardiovascular morbidity of 14/21 and a mortality of 2/21.

In this preliminary report no attempt was made to correlate response rates with the initial tumour stage or grade, since the number of patients was too small for evaluation.

Twelve cyproterone acetate and 11 oestrogen-treated patients with N0/M0 tumours underwent subsequent local high-voltage irradiation after termination of the trial, without additional treatment thereafter, and are under close clinical and histological follow-up. In this group of patients the regression of local tumour mass, resulting in a small lesion subjected to irradiation, is of particular interest from a technical point of view, as size of irradiation field, irradiation time and distribution largely depend on the local extension of the tumour. Follow-up studies are necessary to judge the value of cyproterone acetate in this regard.

In conclusion, we feel that cyproterone acetate is an acceptable and interesting medical alternative in the treatment of advanced prostatic cancer.

Acknowledgements

We are indebted to Prof. Rathgen (Dept. of Gynaecology and Obstetrics, University of Mainz Medical School) for the hormone determinations and to Dr Hohbach from the German Prostate Cancer Registry (Head: Prof. Dhom) for histology studies.

Addendum

Since the submission of this work two publications on the issue are of particular interest Tveter *et al.* (1978) clearly showed that the incidence and severeness of side effects after cyproterone acetate is dose dependent, after the high oral dose of 200 mg serious cardiovascular complications occurred in 6 out of 16 patients, a rate quite different from our series. Bracci (1979) reported on the use of cyproterone acetate in order to assess hormone dependency. The drug was given in a dose of 200 mg orally over 50 to 60 days and local tumour response was used as an index in evaluating androgen sensitivity and for indicating further hormone manipulation.

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Penile Erection Following Complete Spinal Cord Injury in Man

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Summary—Three types of erection following complete spinal transection (at lower thoracic or thoracolumbar levels) in man are described.

Reflex erection involves both corpus cavernosum and corpus spongiosum if the lower level of cord injury or lesional sector (LLLS) is cranial to T10/12, and involves only corpus cavernosum if the LLLS is caudal to T12/L2.

Psychogenic erection may occur when the upper level of cord injury or lesional sector (ULLS) is caudal to T12 and when testicular sensation is normal.

A mixed erection can occur when the ULLS is caudal to T10/12 and the LLLS cranial to S2.

Dejerine (1926) was the first to show that male paraplegics were capable of physiological activity which depended solely upon the spinal cord below the injury. The first study of genitosexual aspects, however, appeared only in 1949 (Guttmann, 1949).

Since 1970 we have examined a number of male paraplegics at their own request in order to help them to regain sexual function and fertility. Results are reported regarding erection only, since ejaculation, orgasm and detumescence all involve more complex mechanisms.

Patients and Methods

One hundred and forty-nine patients were studied. All were paraplegic as a result of injuries received at least 6 months earlier. All had neurologically complete lesions and their ages ranged from 18 to 50 years. None had a previous history of urogenital dysfunction.

Also included in the study were 31 patients who had undergone one of the following procedures: neurotomy, alcohol injection of the trunk or nerve roots, or operations on the lower urinary tract.

Using a standard neurological assessment, an attempt was made to define the limits of the 3 spinal sectors created by the injury (Fig. 1):

1. Lesional sector: the area of spinal cord damaged by injury. The upper limit (ULLS) was defined as the highest cord segment in which pathological signs were present. The lower limit (LLLS) was defined as the segment immediately above the cord segment in which propriospinal activity was present.
2. Supralesional sector: the area of spinal cord where function was normal.
3. Sublesional sector: the area of spinal cord where only propriospinal activity was found after the spinal shock had passed.

Although doubtless of considerable importance, the autonomic nervous system appeared only as a secondary factor in the present work, and in most cases was not systematically studied. In cases where it was, the pilomotor reflex (PMR) was among the clinical criteria chosen, as it seemed to be a simple, reliable technique provided that a distinction was made between the following:

(*a*) the encephalic PMR obtained, for example, by pinching the upper trapezius muscles. The limit of downward PMR diffusion gives a rough idea of the borderline between the supralesional and lesional syndromes, and
(*b*) the spinal PMR obtained, for instance, by repeated painful stimuli in the coccygeal area, which also often trigger somatic contractures: here the upper PMR limit is also the borderline between the lesional and sublesional sectors.

Even with the help of other criteria, it is still difficult to define an autonomic nervous system

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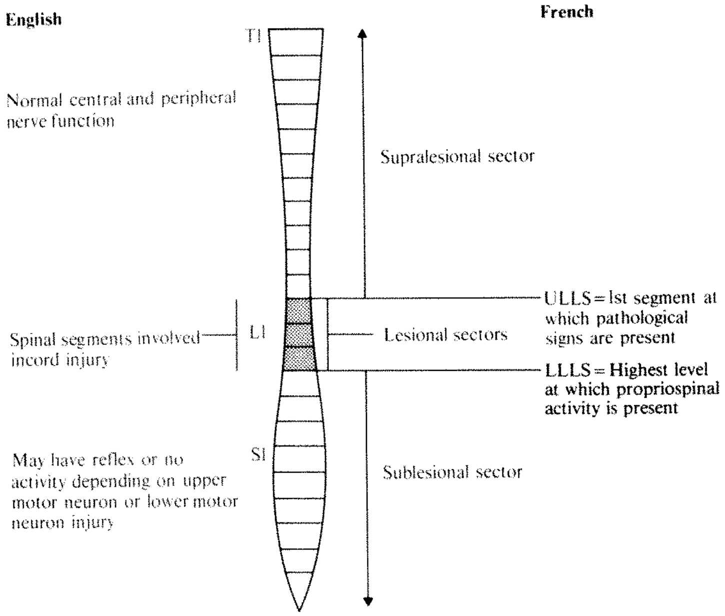
English
French
T1
Normal central and peripheral nerve function
Supralesional sector
ULLS = 1st segment at which pathological signs are present
Spinal segments involved incord injury
L1
Lesional sectors
LLLS = Highest level at which propriospinal activity is present
May have reflex or no activity depending on upper motor neuron or lower motor neuron injury
S1
Sublesional sector

Fig. 1 Definition of terms. Theoretical injury involving 3 spinal cord segments T12/L2.

lesional syndrome and, in most cases, our only guide was an estimate of the function of the peripheral orthosympathetic system.

Results and Discussion

It should be stressed that we had to distinguish between 3 types of erection:

(1) The reflex erection, *i.e.* the erectile response to strictly sublesional cutaneous and/or mucous stimulation which, as we have shown elsewhere, is only present if the conus medullaris is included in the sublesional syndrome.
(2) The psychogenic erection, which is independent of sublesional stimulation. It occurs when the sexual appetite is exacerbated and results only in swelling and lengthening of the penis, without rigidity and therefore without the possibility of intromission.
(3) The mixed erection, which combines both of the preceding mechanisms.

Thus we have excluded 6 patients from the trial because the exact nature of their erections was difficult to determine.

Reflex Erection (Fig. 2)

This occurred in 95 patients whom we divided into 2 groups. The first group consisted of 54 patients who had a true erection involving both the corpus spongiosum and corpus cavernosum: of these, the LLLS was above T12 in 36 cases and below T12 in 18. The remaining 41 patients formed the second group: their erection involved only the corpus cavernosum, with no change in the glans. In this group the LLLS was below T12 in 33 cases and above T12 in only 8.

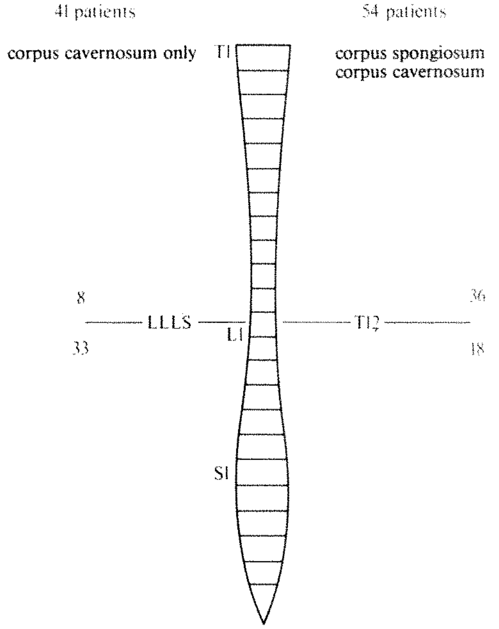

Fig. 2 Reflex erection: 95 patients.

The part played by the spinal cord in the dorsolumbar junction therefore seems obvious and substantiates additional results obtained by a simultaneous study of the autonomic nervous system, although these are too fragmentary to be reported here. Knowing that accurate determination of the LLLS in the cerebrospinal system is subject to error, we are inclined to believe that a satisfactory reflex erection involving both the corpus spongiosum and corpus cavernosum requires the functional integrity of this dorsolumbar spinal cord junction (essentially extending from D10 to L2) both on the cerebrospinal and vegetative levels. On the other hand, when this same spinal cord area is included in the lesional syndrome and, therefore, has to be considered as lacking function in relation to both the cerebrospinal and vegetative systems, the erection in the corpus spongiosum never seems able to achieve the turgescence that normally characterises the pre-ejaculatory phase.

Psychogenic Erection (Fig. 3)

In this connection we studied only the 38 patients whose conus medullaris was part of the lesional sector and who, according to traditional criteria, should not have had any erections.

Nevertheless, 19 of these 38 patients described erections with all of the characteristics of the psychogenic erection: they were brief and not often felt (only 5 cases out of 19). Some were followed by ejaculation (12 out of 19) but the latter was described as premature, spumous and in all cases non-clonal. It could, however, result in pregnancy, as a paraplegic couple proved.

In all of these 19 patients who were able to have a psychogenic erection only, the ULLS was located below T10 and, in 15 cases, below T12. In 8 of the remaining 19 subjects unable to experience any erection, the ULLS was above T10. It thus appears that the efferent factors capable of organising a psychogenic erection usually leave the spinal cord at myelomeres T11 and T12.

It is interesting to compare these results with those recorded for the same patients with respect to testicular sensitivity: all subjects experiencing psychogenic erection had a degree of sensitivity in both testes which may be considered normal, whereas in the other patients it was impaired.

From the clinical point of view, testicular sensitivity therefore seemed to be a good means of assessing the chances of psychogenic erection, no doubt because the necessary afferent factors enter the spinal cord at a level comparable to the one at which the efferent factors making psychogenic erection possible leave it.

Mixed Erection (Fig. 4)

It follows that a mixed type of erection should occur whenever both of the following conditions

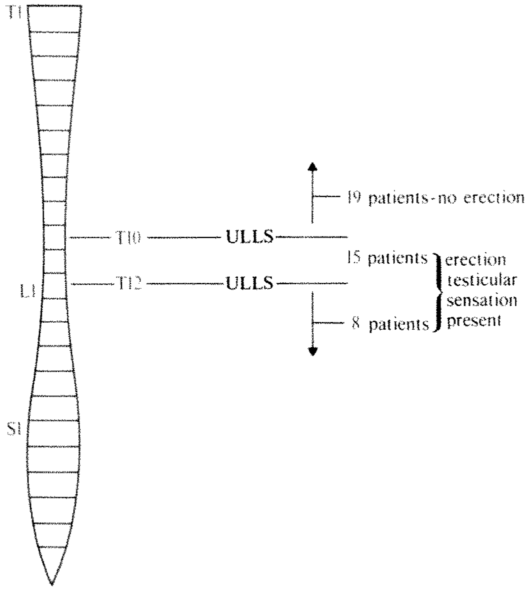

Fig. 3 Psychogenic erection: 38 patients—injury to conus medullaris.

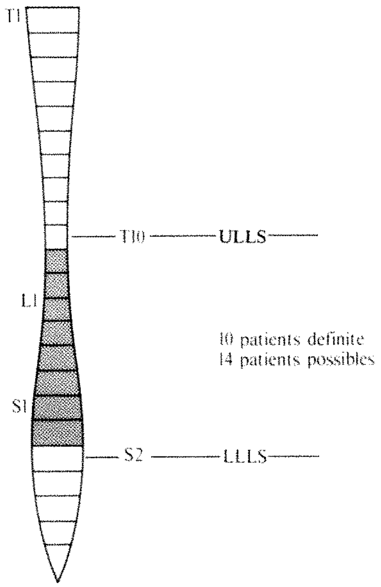

Fig. 4 Mixed erection: 24 patients.

exist: (1) when the ULLS is below T10 and testicular sensitivity is normal (criteria for psychogenic erection), and (2) when the LLLS is above S2, thus permitting reflex erection.

Only 24 of our patients fulfilled these conditions. Of these, 10 spontaneously described a mixed erection which was either psychogenic to start with, and was then intensified by autostimulation, or began as a reflex erection and was strengthened by exacerbation of the libido. Both the duration and the quality of the erections thus obtained varied from one patient to another, but they were always inferior to a normal man's pre-ejaculatory erection, even though intromission was usually possible.

In the case of 14 patients who fulfilled the conditions for mixed erection but did not spontaneously describe this, we did not wish to question them too closely and were therefore unable to ascertain whether in fact they did have mixed erections. However, it is very unlikely that such erections were really experienced by all of them. The autonomic system undoubtedly plays an important part here, although we were only able to examine it sporadically and inadequately.

It is concluded that paraplegics with a stabilised, complete spinal cord section syndrome may experience 3 types of erection:

(1) The reflex erection produced by sublesional stimulation. This is the only type able to activate both the corpus spongiosum and the corpus cavernosum and appears possible whenever the lesional syndrome does not extend below T10 or T12. A reflex erection remains possible if the syndrome's lower limit is located further down, provided that the lesion does not affect the spinal cord conus. In that case, however, the corpus spongiosum may no longer be involved.

(2) The psychogenic erection, in which exacerbation of the libido causes lengthening and swelling of the penis but does not usually permit intromission; the latter is possible when the lower dorsal spinal cord is supralesional, which in practice means when testicular sensitivity is normal.

(3) A mixed type of erection, very often reported by patients with a lesional syndrome whose upper limit is located at T12 or below, and whose lower limit is at S2 or above.

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Transurethral Drainage of the Seminal Tract for Obstruction, Infection and Infertility

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Summary—The clinical condition of obstruction of the ejaculatory ducts and seminal vesicles is described; it may be suspected from the symptoms, and the diagnosis subsequently confirmed by radiology.

The method of treatment by transurethral incision or resection is described; the results were encouraging and it is suggested that this neglected clinical problem should receive more attention by urologists.

Obstruction of the seminal tract may be complete or partial. In complete obstruction, azoospermia is found, whereas in partial obstruction, oligozoospermia is the usual result.

Obstruction of the ejaculatory ducts can be treated by dilatation of the duct orifices, lavage of the seminal vesicles through the duct orifices (Lowsley and Kirwin, 1944) or lavage through the vas deferens (Belfield, 1913). Massage of the prostate gland and the seminal vesicles may express retained secretions (Lowsley and Kirwin, 1944). Limited transurethral resection of the dorsal part of the prostate gland (Farley and Barnes, 1973; Porch, 1978) improves drainage from the seminal vesicles and, similarly, a transurethral prostatectomy improves vesicular drainage by virtue of the fact that the ejaculatory ducts are removed with the prostatic tissue.

Obstructed seminal vesicles can be drained by incision or resection of the ejaculatory ducts, and this procedure will be described.

Patients and Methods

The case histories of 7 patients will be described. Typical features in this group were:

1. Either azoospermia or oligozoospermia.
2. Pain in the testicles, pubic area, perineum or penis, aggravated by sexual intercourse.
3. Recurrent epididymitis and prostatitis showing ejaculatory duct obstruction.

Radiological Investigation

A vasovesiculogram was done to establish the diagnosis: the vas deferens was exposed in the scrotum and a teflon intravenous cannula was introduced into its lumen either by puncture or by incision of the vas. A water soluble contrast material was injected to outline the seminal vesicles. The normal seminal tract requires 2 to 3 ml of contrast to outline each side and some contrast will pass into the bladder. Obstructed vesicles require more contrast to fill them.

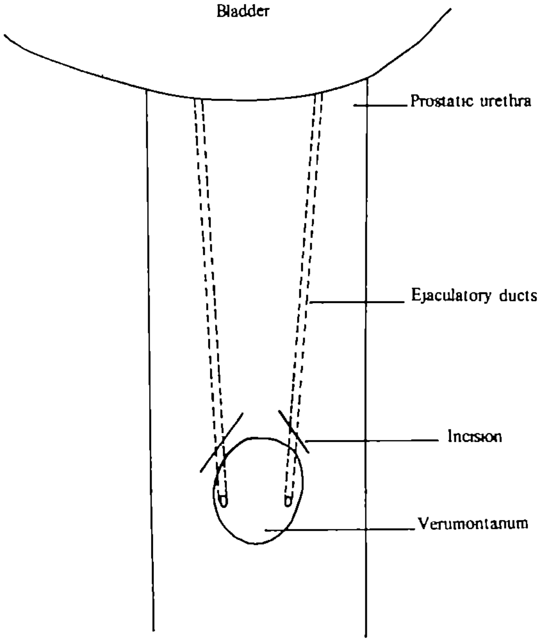

Fig. 1 Transurethral incision across the ejaculatory ducts.

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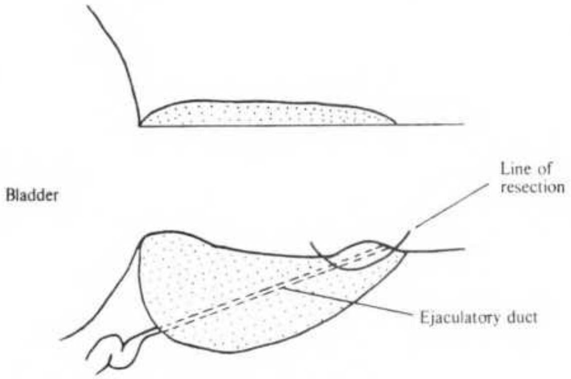


Fig. 2 Resection of the verumontanum.

Transurethral Incision or Resection

The incision was made with either a Collings knife or a similar rigid electrode, through a panendoscope, across the ejaculatory ducts on each side just proximal to the verumontanum (Fig. 1). The incision can also be made with the loop electrode of a resectoscope. Resection of the ejaculatory ducts was accomplished with a loop electrode, by resecting the verumontanum (Fig. 2). The incision commenced just proximal to the verumontanum and removed the whole structure.

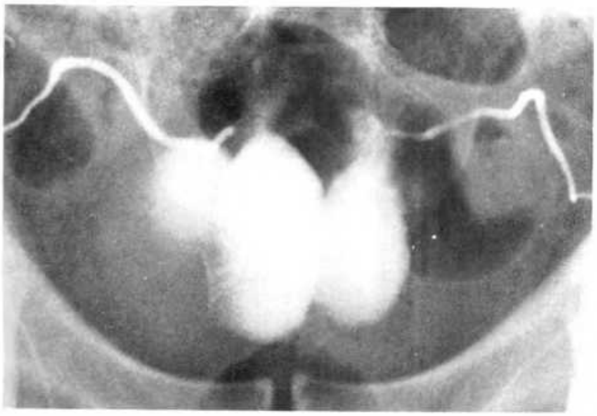
Care must be taken not to injure the external urethral sphincter. Resection can also be confined to the right or to the left duct orifice. Incision and resection of the ducts should be done at the time of vasovesiculography as it is then possible to inject methylene blue through the cannulae in the vasa, and to observe, through the incision, its exit in the prostatic cavity. This ensures that the incision has been made deep enough to reach the ejaculatory ducts.

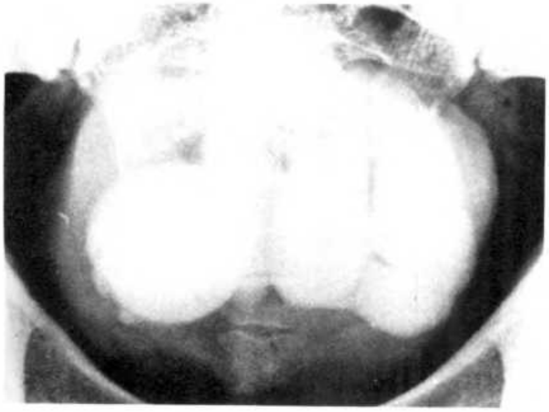
Case Reports

Case 1

A 38-year-old man was infertile. Three sperm counts were less than 1 million ml. He had large testicles and biopsy showed normal spermatogenesis. A vasovesiculogram revealed obstruction in the vesicular part of his seminal tract (Figs. 3a, b, c). The seminal vesicles were grossly sacculated. Cystoscopically they produced 2 bulges in the bladder base. The prostatic urethra and verumontanum were normal.

A slightly oblique incision 0.5 cm long was made with a Collings knife electrode in the prostatic urethra, just proximal to the verumontanum across the midline, and the seminal tract entered about 0.2 cm below the mucosal surface. A large quantity of milky fluid gushed out of the incision.





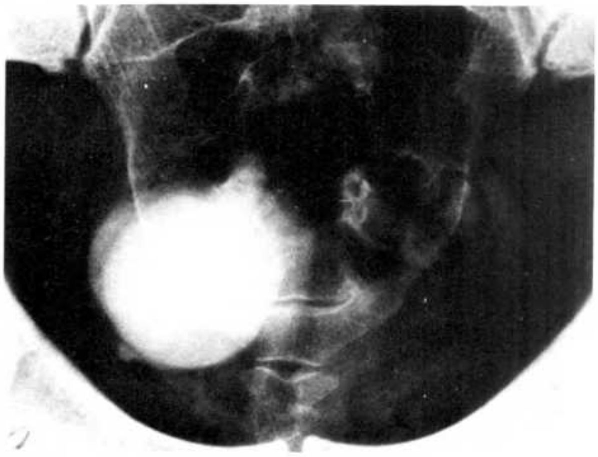


Fig. 3 (a) The seminal vesicles are partly filled with contrast. The vasa are grossly dilated. (b) After 5 h the contrast has diffused throughout the huge vesicles and bladder. (c) Six days later contrast was still present on the right side.

Table

Date	*Vol. (ml)*	*Count*	*Motility*		*Morphology*
			IMM	*24 h*	
Case 1					
17 July 1971	2.0	100,000	UA		X
17 February 1972					XX
15 March 1972	2.5	0			
12 July 1972	2.0	2,000,000	SM	0	
11 October 1972	0.5	3,000,000	20% MM	0	HP Ab
5 February 1973	1.5	6,000,000	SM	0	EI
11 October 1973					XXX
23 November 1974	2.5	23,500,000	10% PM		51% Normal
7 April 1975	3.5	3,000,000	0		
8 November 1975	2.0	13,000,000	10% SM	0	
29 April 1976	1.0	13,000,000	40% PM	0	HP Ab
1 July 1976	1.0	30,000,000	50% PM	0	Normal
26 May 1977	2.0	43,000,000	30% PM	0	Normal
24 August 1978	2.0	17,000,000	50% PM		51% Normal
Case 2					
2 May 1975		3,500,000	40% PM	5%	
2 March 1976	1.1	11,500,000	45% PM	25%	26% Ab
Case 3					
April 1976	2.5	70,000,000	40%		

UA	Unable to assess.
X	Three pre-operative sperm counts were identical.
XX	Vasovesiculography and transurethral incision.
XXX	Birth of child.
IMM	Immediate.
SM	Sluggish motility.
MM	Moderate motility.
PM	Progressional motility.
HP Ab	High proportion abnormal forms.
EI	Excess immature forms.

Following this procedure the sperm count increased steadily and 18 months later a baby girl was born; 4 years after the incision the sperm count had reached 43 million (Table).

Case 2

A 23-year-old man was infertile. His sperm count was 3.5 million/ml. Physical examination revealed no abnormality.

The seminal vesicles were not palpable. Serum follicle stimulating hormone was 0.9 ng/ml and luteinising hormone was 1.4 ng/ml.

Vasography showed large saccular seminal vesicles with huge ejaculatory ducts (Fig. 4). Each ejaculatory duct was incised with a Collings knife electrode through a panendoscope. After 10 months the sperm count was 11.5 million/ml and he stated that he ejaculated a larger volume of semen (Table).

Case 3

A 32-year-old man had been married for 8 years and

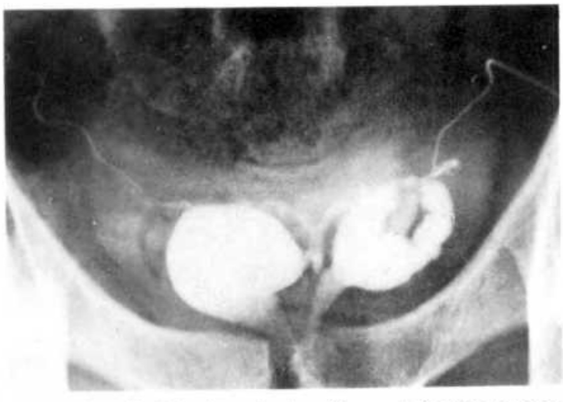


Fig. 4 Grossly dilated seminal vesicles and ejaculatory ducts. The vasa and ampullae are not dilated.

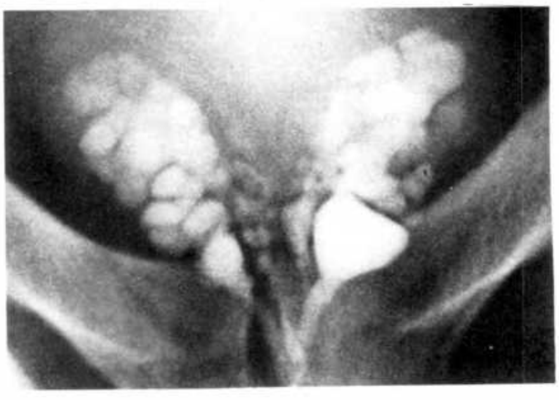


Fig. 5 Grossly dilated seminal vesicles and ejaculatory ducts. The ampullae and vasa are slightly dilated.

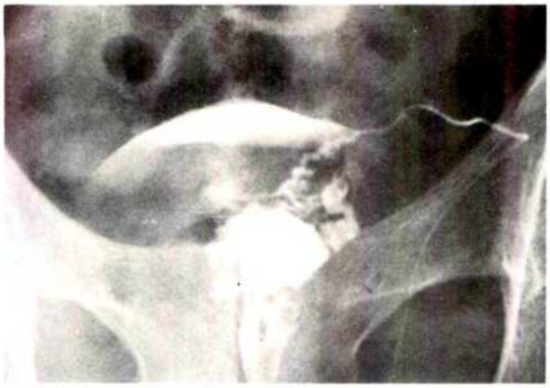


Fig. 6 A vasogram on the left side fills an abscess cavity in the seminal vesicle and prostate gland.

had a child aged 5 years. No further pregnancies occurred although his sperm count was 70 million/ml (Table). Physical examination revealed no abnormality and the seminal vesicles were not palpable. Vasography showed that he had dilated saccular seminal vesicles and dilated ejaculatory ducts (Fig. 5). The ejaculatory ducts were incised with the loop electrode of a resectoscope.

Small biopsies were obtained from the verumontanum and these showed oedema and congestion histologically. Testicular biopsy showed normal spermatogenesis. Ten months later his wife had a baby girl and 13 months after that another girl was born. Post-operative sperm counts are not available.

Case 4

A male aged 52 years had left-sided epididymitis and cystitis. Rectal examination revealed an indurated seminal vesicle on the left side. A vasogram was done on the left side and the contrast filled a cavity in the left seminal vesicle and the prostate gland (Fig. 6). Cystoscopy showed congestion and oedema of the left side of the trigone and a very congested prostatic urethra. Pus oozed out of the left ejaculatory duct orifice and probing revealed an abscess cavity 2 cm long, lying just proximal to the verumontanum.

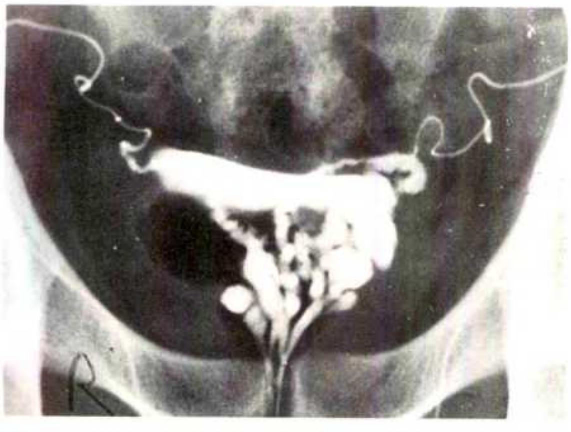


Fig. 7 The right seminal vesicle does not fill completely and the ampulla of the vas on the right side is considerably dilated. The ejaculatory ducts are normal and contrast is present in the bladder.

Case 5

An unmarried man aged 21 years had had continual pain in the right testicle for 2 years.

The pain became very acute during ejaculation. Vasography showed enlargement of the ampulla of the vas on the right side and incomplete filling of the right seminal vesicle. The ejaculatory ducts were normal (Fig. 7). The verumontanum was resected and following this he was relieved of all pain.

Histological examination of the verumontanum showed fibrous tissue, round cell infiltration, corpora amylaceae and a small focus of calcification. He subsequently married and had 2 children.

Case 6

A male aged 37 years complained of being infertile. He had been injured in a train accident at the age of 19 years and sustained a crush injury of the pelvis and left leg. Since then he had been unable to ejaculate, whereas he could do so before. Physical examination revealed normal genitalia and a normal prostate gland. The seminal vesicles were not palpable. Vasography showed obstruction of the ejaculatory ducts with dilatation of the seminal vesicles, ampullae and vasa on each side. Contrast passed into the bladder. Prostatic massage produced large amounts of whitish fluid from both ejaculatory ducts, seen on panendoscopy. The vesicles

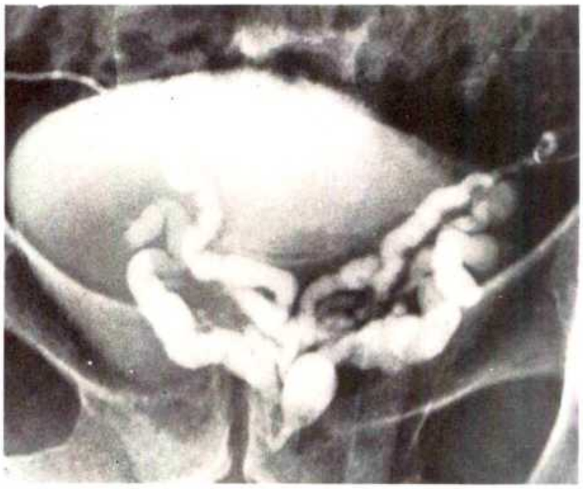


Fig. 8 Grossly dilated vasa, ampullae and seminal vesicles. The right seminal vesicle has not filled completely. Contrast is present in the bladder.

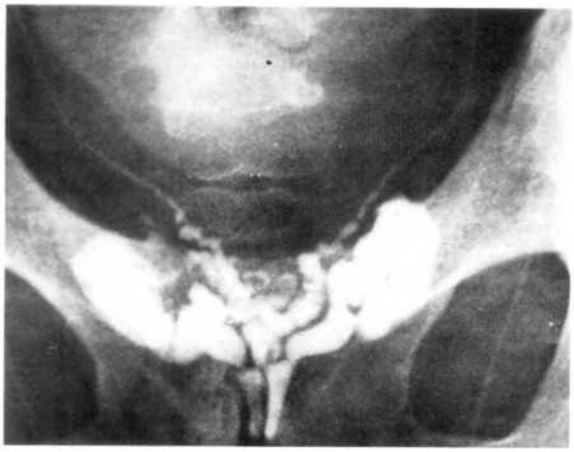


Fig. 9 The ejaculatory ducts and seminal vesicles are dilated.

were washed out by lavage through the cannulae in the vasa deferentia in the scrotum. There was no improvement in his symptoms. He returned 3 years later with the same complaint. A vasogram was repeated on each side (Fig. 8) and the appearances were identical with those done 3 years earlier. The verumontanum, which had a normal appearance, was resected by removing one loopful of tissue and new, wide openings were created in the ejaculatory ducts. This was demonstrated by injecting methylene blue through the cannulae in the vasa in the scrotum. Histological examination of the verumontanum showed benign prostatic tissue in which corpora amylaceae were present. Six weeks later he stated that he was ejaculating a small amount of fluid. This continued for a few months but when a sperm count was requested 6 months later he indicated that he was no longer ejaculating. He was, however, relieved of some symptoms and a vague discomfort, which had occurred previously in the testicles and penis after intercourse, disappeared completely. The climax did not come so quickly, lasted longer and intercourse was more satisfactory.

Case 7

A male aged 39 years was seen in 1975. He had 4 children and requested a vasectomy. He also complained of a continuous burning sensation in the glans penis, urinary frequency and incomplete bladder emptying. He had a strong stream if he forced his urine out. Physical examination of the abdomen, genitalia and prostate gland was normal. The urine was clear. Vasography showed dilated ejaculatory ducts with obstruction at the duct orifices and dilatation of the seminal vesicles. Cystoscopy showed normal appearances in the bladder except for a prominent median bar. The bladder neck was incised cystoscopically at 3 and 9 o'clock and vasectomy was carried out.

He was improved for a few months but returned a year later with similar symptoms. A transurethral prostatectomy was carried out, removing 10 g of prostatic tissue. Microscopic examination of the tissue showed benign nodular hyperplasia. Following this procedure he had an excellent urinary stream but continued to complain of burning in the glans penis and in the perineum. He still had a sensation of incomplete bladder emptying.

He was seen again in March 1979 and complained of continual pressure in the perineum for 2 years. It felt as if he had "a brick sitting there, day and night". After the ejaculation of semen he had more pain in the perineum and glans penis, which lasted an hour and felt hot, as if he had a poker there. He was afraid of having sexual intercourse.

Vasography showed obstruction of both ejaculatory duct orifices with dilatation of the ducts and seminal vesicles (Fig. 9). At cystoscopy the bladder was normal and the prostatic cavity well excavated, with a wide bladder neck. The verumontanum was normal. Methylene blue was injected into the vasa and its exit observed through the ejaculatory duct orifices on each side on the verumontanum. The verumontanum was resected with a resectoscope, creating new openings of the ejaculatory ducts 1 cm proximally, through which methylene blue flowed. The resected tissue showed benign prostatic hyperplasia with concretions in some of the glands. A chronic inflammatory cell infiltrate was present. The next day the pressure in the perineum was no longer present.

Four months later he stated that he was completely relieved of the perineal pressure and the pain following intercourse.

Discussion

Dilatation and obstruction of the seminal tract have often been found in patients investigated for infertility and genitourinary infection (Weintraub, 1976). It was felt that, in many cases, ejaculatory duct obstruction was present. Physical examination rarely revealed any abnormality of the seminal vesicles.

Obstruction of the ejaculatory ducts results in dilatation of the seminal tract and it may involve the seminal vesicle, ampulla of the vas, the whole of the vas deferens and the epididymis (Figs. 3, 5, 8).

The obstruction is frequently confined to the seminal vesicle and the ejaculatory duct (Fig. 4) with sparing of the ampulla and vas deferens, suggesting a protective sphincteric mechanism where the ampulla of the vas joins the seminal vesicle. A "sphincter spermaticus" has been described around the ejaculatory ducts (Farley and Barnes, 1973). In obstruction, the ejaculatory duct enlarges in continuity with the seminal vesicle

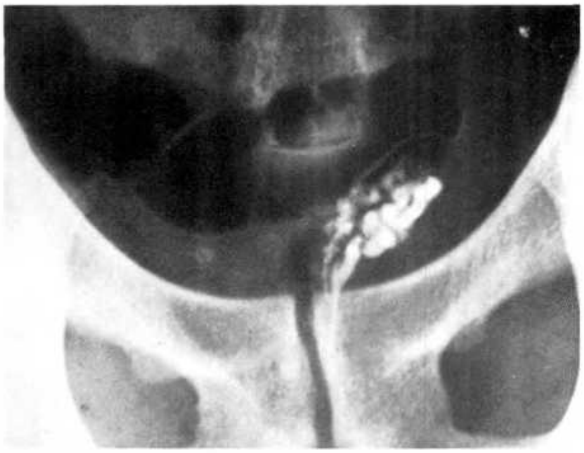


Fig. 10 A normal vasogram. The appearance of the ejaculatory duct suggests that it is the duct of the seminal vesicle. Compare Figures 4 and 5.

(Figs. 4, 5) and the ampulla of the vas deferens appears to be a tributary of the seminal vesicle. This has also been demonstrated when the radiological anatomy has been normal (Fig. 10).

These appearances support the concept that the ejaculatory duct is the duct of the seminal vesicle and that the vas deferens drains into the vesicle (Lowsley and Kirwin, 1944). For this reason it is sufficient to incise the ejaculatory duct in order to drain an obstructed seminal vesicle. It is not necessary to incise or resect through the prostatic capsule to reach the vesicle.

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Effects of Amitriptyline on Semen of Infertile Men

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Summary—A clinical evaluation of the effects of the antidepressive drug amitriptyline on the semen of 20 infertile men with oligoasthenozoospermia was carried out. Quantitative assessment of semen in the whole group showed significantly higher sperm counts, an increased proportion with normal sperm morphology and an increased semen volume after treatment, with a high positive correlation between sperm count before and after treatment. Individual qualitative evaluation showed an increased sperm count in 50% and increased motility in 35% of patients. It would seem that amitriptyline has a beneficial effect on semen in some of these patients.

In spite of intensive diagnostic studies, there are still many patients in whom a specific cause for persistent oligoasthenozoospermia cannot be found. Although several methods of treatment have been evaluated in this group of infertile men, the results are generally disappointing. Since it has been reported that male fertility may be affected in tense and depressed patients (Davis *et al.*, 1966; Stewart, 1966; Macleod, 1972; Padrón, 1972) and reproductive capacity may be improved by some drugs with an antidepressive effect (Blair and Kline, 1962; Davis *et al.*, 1966; Stewart, 1966; Vogel and Braun-Falco, 1971), we have carried out a trial of treatment with amitriptyline in infertile men with oligoasthenozoospermia.

Materials and Methods

We studied 20 consecutive patients with oligoasthenozoospermia, aged between 23 and 41 years, who had a history of infertility of at least 2 years' duration. All patients underwent a general examination and none of them showed clinical evidence of urological, endocrine or metabolic abnormalities. At least 2 basal semen samples, obtained after 3 to 5 days' abstinence, were analysed for ejaculate volume, sperm count, motility and morphology (Eliasson, 1971; Padrón, 1972). No attempt was made to evaluate the psychiatric status of the subjects since psychological repercussions are inevitable following the mere revelation of the existence of infertility in the male (Walker, 1977).

Patients were given 25 mg of amitriptyline twice daily orally for a period of 2 to 3 months. Semen analyses were carried out at 2 to 3 months and 4 to 5 months after starting the treatment, by a technician who was not aware of the patients' treatment. Testicular biopsy (Paramio *et al.*, 1974) was performed before therapy in 15 patients. The histological features were those of hypospermatogenesis and consisted of sloughing of immature cells, disorganisation and/or diminished numbers of germinal cells and variable thickenings of the tubular wall. No morphological changes were observed in the interstitial tissue.

Wilcoxon's signed rank test (Langley, 1970) was used to compare the highest values of the basal semen analysis data with the highest values obtained during or after treatment. Correlations between the baseline sperm count and sperm count achieved after starting treatment were calculated using Pearson's product moment correlation formula with a Novus 6035 computer. Furthermore, for qualitative evaluation of the therapeutic effects of amitriptyline we adopted the following arbitrary criteria:

1. Marked improvement: increase in sperm count $\geq 20 \times 10^6$/ml and in motility and normal morphology $\geq 30\%$.
2. Moderate improvement: increase in sperm count $\geq 10 \times 10^6$/ml but $< 20 \times 10^6$/ml, and increase in motility and normal morphology $\geq 20\%$ but $< 30\%$.
3. Minimal improvement: increase in sperm count $\geq 5 \times 10^6$/ml but $< 10 \times 10^6$/ml and increase in motility and normal morphology $\geq 10\%$ but $< 20\%$.

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Table 1 Effects of Amitriptyline Treatment on Semen Quality in Infertile Men with Oligoasthenozoospermia

Patient No.	Baseline				After treatment			
	Sperm count (10^6/ml)	*Motility (%)*	*Morphology (% normal)*	*Semen volume (ml)*	*Sperm count (10^6/ml)*	*Motility (%)*	*Morphology (% normal)*	*Semen volume (ml)*
1	Scanty	0	—	4.0	11.5	70	60	5.5
2	0.3	0	—	2.5	24.5	15	55	1.8
3	0.3	0	—	4.0	35.3	40	50	3.6
4	0.5	0	—	10.0	2.0	0	—	10.5
5	0.5	0	—	5.5	19.0	45	45	6.5
6	0.7	0	—	5.5	0.5	0	—	6.0
7	0.9	0	—	5.0	0.1	0	—	4.5
8	1.0	0	—	3.5	2.0	0	—	5.6
9	1.2	5	—	3.8	8.5	20	35	5.2
10	2.0	5	—	3.6	6.5	20	42	4.6
11	2.5	5	—	2.5	19.0	40	49	5.7
12	4.0	5	32	2.8	33.5	15	50	4.7
13	4.5	0	39	3.5	3.0	5	30	3.5
14	6.5	15	22	4.2	5.0	25	38	5.5
15	8.5	0	30	2.8	10.5	0	50	2.4
16*	10.0	10	35	2.5	40.0	40	44	2.0
17	11.5	30	32	2.0	7.0	40	40	2.9
18	11.5	0	42	8.0	81.0	30	50	9.0
19	12.5	5	46	3.0	28.5	30	57	5.6
20	30.0	5	50	6.0	69.0	5	48	7.0

* Pregnancy.

— = Data not recorded in samples with sperm count $<3\times10^6$/ml.

4. Nil: when the increase in sperm count was $<5\times10^6$/ml.

The pregnancy rate was not used as an index to evaluate the treatment because the follow-up was relatively short and some gynaecological and endocrine abnormalities were observed in some of the wives.

Results

The baseline sperm counts, motility, morphology and semen volume and the values after starting treatment with amitriptyline are shown in Table 1. There was a significant increase in sperm count and motility with treatment ($P<0.002$). Semen volume and sperm morphology were also significantly improved after treatment ($P<0.05$). There was a highly significant positive correlation ($r=0.647$, $P<0.01$) between sperm counts before and after treatment. Individual qualitative evaluation of sperm count and motility showed that 50% of the patients demonstrated improved sperm count and 35% improved motility (Table 2). Pre-treatment sperm counts in the patients who improved were less than 1 million/ml in 5, less than 5 million/ml in 5 and less than 15 million/ml in 4. The maximal increase observed was 69.0 million/ml in sperm count and 70% in motility. One pregnancy resulted when the patient achieved a normal sperm count. No clinical side effects were observed.

Discussion

Several non-specific remedies have been assessed in infertile men with idiopathic oligoasthenozoospermia, since this condition is one of the more frustrating problems in medicine. Some reports have claimed that male fertility may be influenced by psychotropic drugs and improvement in semen quality has been reported with the use of phenothiazine derivatives (Stewart, 1966) and monoamine-oxidase inhibitors (Blair and Kline, 1962;

Table 2 Qualitative Evaluation of Sperm Count and Motility After Amitriptyline Treatment

Qualitative evaluation	*Sperm count*		*Motility*	
	No. of patients	*%*	*No. of patients*	*%*
Marked improvement	6	30	6	30
Moderate improvement	4	20	1	5
Minimal improvement	1	5	6	30
Nil	9	45	7	35

Davis *et al.*, 1966). More recently, Vogel and Braun-Falco (1971) reported an increase in sperm counts and semen volumes in patients with oligozoospermia treated for 28 days with amitriptyline.

Under the conditions of this study, amitriptyline treatment of infertile men with oligoasthenozoospermia resulted in quantitative semen improvement. We confirmed the results in sperm count and semen volume observed previously but we also observed an improvement in sperm motility and morphology. Individual qualitative evaluation of semen response showed that half of the patients demonstrated an improved sperm count and approximately one-third an improved motility. In the present study, individual increase in sperm count occurred in an unpredictable fashion since it was seen in patients with different pre-treatment values, but it seems that the prognosis is related to the severity of the oligozoospermia.

It has been demonstrated that most patients with sperm counts less than 10×10^6/ml, motility less than 40% and normal morphology less than 40% have values which remain consistently below those levels in subsequent visits (Sherins *et al.*, 1977). In most of our patients the baseline semen analysis parameters were lower than the characteristics described above, and therefore it is likely that the changes observed after treatment were the effects of the treatment. However, because of the well-known problems in the interpretation of changes in semen analysis, this work has now been extended to a double blind controlled clinical trial.

Acknowledgements

We express our appreciation to Dr M. Pérez-Plaza and staff who performed the semen analyses The authors wish to thank Mrs J Volfsbergs for typing the manuscript.

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Case Reports

An Unusual Presentation of Chronic Extravasation of Urine

D. JAGADISAN, G. RAJENDRAN, V. K. JEEVARATHNAM and R. PRABAKAR, *Department of Urology, Stanley Medical College, Madras 600 001, India*

A case is described of intrapelvic rupture of the urethra with chronic extravasation of urine into the thigh

Case Report

An 18-year-old male was admitted in May 1977 complaining of difficulty in passing urine and of swelling in the upper part of the left thigh. Two months previously he had injured the perineum and had noted bleeding from the urethra, but received no treatment. Gradually he developed a swelling in the thigh and had difficulty in passing urine. The swelling increased in size when he strained and he passed more urine through the urethra when he compressed it.

Examination revealed a globular cystic swelling in the upper part of the medial aspect of the left thigh (Fig.) and a distended bladder 6 cm above the pubic symphysis. There was no swelling in the scrotum or perineum. Manual compression of the swelling resulted in dribbling of urine through the external meatus. The prostate was soft and tender.

The blood urea was 6 mmol/l and the serum creatinine 8.8 mmol/l. The urine contained *Esch. coli* sensitive to ampicillin, kanamycin and gentamicin. Plain X-ray showed a fracture of the left inferior ramus of the pubis with a soft tissue swelling over the upper medial part of the left thigh.

An IVP showed mild bilateral hydronephrosis with a distended bladder. Retrograde urethrogram showed extravasation into the pelvis and thigh swelling.

Two days after admission a suprapubic cystostomy was carried out and the thigh swelling drained. One month later the stricture in the posterior urethra was dilated and the suprapubic tube removed.

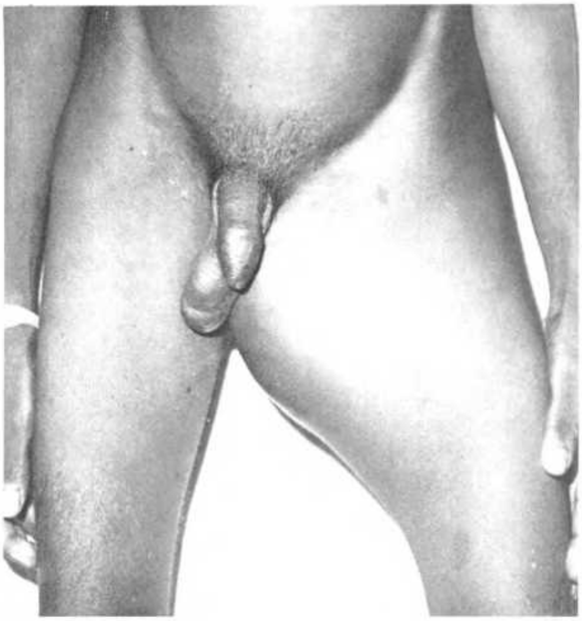

Fig.

Comment

Following posterior urethral injuries extravasated urine may track through the obturator foramen into the thigh.

Requests for reprints to: 26/3, Sait Colony, 2nd Street, Madras-8, South India.

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Malignant Phaeochromocytoma of the Urinary Bladder

P McR HIGGINS, *North Staffordshire Hospital Centre, Stoke-on-Trent* and G C. TRESIDDER, *The London Hospital, London*

Little is known about the prognosis of this rare tumour (Javaheri and Raafat, 1975), and so it is felt appropriate to provide further follow-up findings in a case first reported 14 years ago (Higgins and Tresidder, 1966).

Follow-up of Case 1 (1966)

In our paper of 1966 we described, as Case 1, a 15-year-old male who presented with haematuria and clot retention. At that time his blood pressure with a distended bladder was 160/120 mmHg and his urinary 4-hydroxy, 3-methoxy mandelic acid excretion was 13.7 mg/24 h. In January 1965 a partial cystectomy was performed. Histological examination showed a well-differentiated phaeochromocytoma. However, there was lymphatic permeation and, in an enlarged internal iliac node, metastatic tumour was present. A lymphangiogram suggested replacement of some para-aortic lymph nodes by neoplasm and a course of Cobalt-60 irradiation to a tumour dose of 4000 rads was given to the abdomen and pelvis. Post-operatively, the 4-hydroxy, 3-methoxy mandelic acid excretion rate was 3 mg/24 h.

The patient remained well with blood pressure and micturition both normal. Follow-up was made difficult by his leaving our district. He remained in good health for 8 years until November 1973 when, after experiencing haematuria for a week, a cystoscopy was performed which showed a lesion measuring 0.75 cm in diameter on the right side of the bladder. It was described as being red, like a granuloma and partly covered by flakes of mucoid material. Biopsy showed tumour which on review contained areas similar to the morphology of the original operative specimen from the partial cystectomy in 1965. At this time his blood pressure was 130/90 but the urinary excretion of 4-hydroxy, 3-methoxy mandelic acid was 9.3 mg/24 h.

Once more the patient moved to a new district and was not seen again until April 1975 when, following further haematuria, another partial cystectomy was performed. At this operation the tumour involved the dome and anterior wall and was found to be adherent to the posterior surface of the pubis. A post-operative course of Cobalt-60 irradiation (4500 rads in 20 treatments over 30 days) was given to the region of the symphysis pubis. Histological examination of the operative specimen on this occasion showed tumour penetrating the full thickness of the vesical wall. There were "pockets" of adrenal medulla-type cells in a very vascular stroma, with appearances similar to those of the original partial cystectomy specimen showing the morphology characteristic of phaeochromocytoma. However, the histochemical stains for secretory granules were negative. The patient made a good recovery from this operation and cystoscopies in February and August 1976 showed no sign of recurrence—there was scarring at the site of the excision. No mass was palpable bimanually and the patient was well, with normal blood pressure.

Comments

In a follow-up of 138 cases of phaeochromocytoma treated at the Mayo Clinic, Remine *et al.* (1974) reported a 5-year survival rate for 96% of patients with benign tumours and 44% of those with malignant ones. On the whole, it seemed that survival was poorer in patients with malignant extra-adrenal tumours than in those where the tumour originated in the adrenal gland itself, but nonetheless they felt that even patients with recurrent tumour occasionally enjoyed long survival and they suggested where possible recurrences should be excised, both in order to control hypertension when present, and in the hope of extirpating the tumour.

This case certainly seems to demonstrate the point since no recurrence was found until 9 years after the tumour was first diagnosed and treated, and treatment of the recurrence appears to have been satisfactory at least for the time being.

Acknowledgements

We are most grateful for the help we have received, in completing this follow-up, from Dr J. S. Howell, Dr M. Marlborough and Mr J. H. E. Verdon of Poole General Hospital, Dorset.

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Points of Technique

A Method of Post-operative Irrigation in Transurethral Resection

J. M. TOWLER, MA, BM, BCh, FRCS, *Senior Registrar, Department of Urology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen.* (Now Consultant Urological Surgeon, Luton and Dunstable Hospital)

This method is an adaptation of the technique in general use for the introduction of urethral catheters for measurement of intravesical pressure during urodynamic studies. The catheter used for irrigation is a 7.5 FG infant feeding tube and it is placed in the prostatic cavity in the following way:

An introducer is put into a 22 FG Foley plastic catheter and the infant feeding tube is pushed into one of the side holes so that it is gripped and held there while the catheter is passed (Fig. 1).

When the catheter is in the bladder, the feeding tube is pulled gently until it has disengaged from the side hole; there is a slight "give" when this happens.

The introducer is then removed, the balloon inflated and the 2 catheters pulled out together until the balloon impacts at the bladder neck.

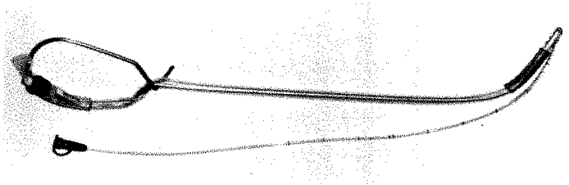

Fig. 1 Method of fixation of infant feeding tube prior to insertion into bladder with inset showing tube in the side drainage hole of the urethral catheter.

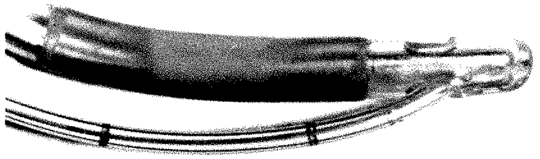

Fig. 2 Inset to Figure 1.

The exposed parts of the catheters are dried and held together with plastic adhesive strapping (Fig. 2).

Irrigation is commenced using saline and an intravenous giving set.

The 7.5 FG infant feeding tube gives much greater flow rates than the irrigation channels of the 3-way catheters available. For a given head of pressure the ratio is almost 3:1. There has been no difficulty in introducing the tubes and there is no reason why larger ones should not be used, if this is desired. The method utilises standard equipment which is readily available. It has been used in addition to frusemide-induced diuresis in cases of marked haemorrhage following transurethral resection and has reduced the need for bladder lavage.

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Author's Follow-up

The Treatment of Interstitial Cystitis by Cystolysis with Observations on Cystoplasty. A Review after 7 Years

P. H. L. WORTH, *Department of Urology, University College Hospital, London*

In our original paper we discussed the place of cystolysis in the management of interstitial cystitis when the bladder had a capacity of at least 400 ml under general anaesthesia (Worth and Turner-Warwick, 1973).

I have continued to use this technique, obtaining good symptomatic improvement in the majority of patients. I have tried extending its use in, for example, the patient with a sensitive and painful bladder whose type of chronic cystitis differs histologically from interstitial cystitis. This group has included 2 men. I have also used the technique in patients with severe frequency and a cystoscopically normal bladder (usually with an above average capacity) and who also have an incontinence problem. Although it is relatively easy to combine this technique with a suprapubic repair procedure, the results are unsatisfactory because the denervation cannot really affect the trigone.

I think it is fair to say that in urological practice the type of patient who might benefit from the operation is seen infrequently. It is likely that such patients have already had a considerable number of different medications (often including steroids), usually administered systemically rather than intravesically.

These patients are very symptomatic, with pain and frequency. When drug treatment has failed, the alternatives to cystolysis are either cystoplasty or diversion. The technique of cystolysis has not altered and remains relatively simple; morbidity is low and the procedure does not compromise any subsequent surgery. The results remain unpredictable in the long term, but in the short term pain becomes negligible and as a result frequency is much reduced.

If symptoms return post-operatively, further cystoscopy should be undertaken. It is always possible that the bladder capacity has diminished and this may occur because the blood supply to the dome has been too severely compromised—hence care should be taken during operation to preserve at least one superior vesical artery.

As the next procedure I would recommend cystoplasty (preferably caecocystoplasty) rather than diversion, since cystoplasty in interstitial cystitis gives excellent results.

Reference

Worth, P. H. L. and Turner-Warwick, R. (1973). The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. *British Journal of Urology*, **45**, 65-71.

Conferences and Courses

South African Biennial Urological Congress

Durban, South Africa. 10-15 August 1980.

Further particulars from: F. Nel, Hon. Secretary, The Urological Association of South Africa, P.O. Box 37287, Overport, 4067, Durban, South Africa.

Edinburgh Urological Festival

Edinburgh. 1-3 September 1980.

A postgraduate course in urology for consultants, senior registrars and registrars. The topics to be covered include: unstable bladder, urethral syndrome, prostatitis, equivocal obstruction, upper and lower tract tumours, investigative techniques, calculi.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG, Scotland, UK.

Manchester and North West Region Kidney Research Association. One-Day International Symposium on Idiopathic Hydronephrosis

Manchester. 5 September 1980.

Registration fee £15.00. Further particulars from: P. H. O'Reilly, Department of Urology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

32nd Meeting of the German Society of Urology

Berlin, Germany. 10-13 September 1980.

Further information from: Professor R. Nagel, Urologische Klinik der Freien Universität, Klinikum Westend, 1000 Berlin 19, Germany.

Swiss Society of Urology: 36th Annual Meeting

Montreux, Switzerland, 16-18 October 1980.

Further particulars from: Prof. K. Bandhauer, Secrétaire de la SSU, Clinique urologique, Hôpital cantonal, CH-9007 St-Gallen.

First Meeting. Urological Days of Necker

Paris, France. 12-14 March 1981.

The topics are:

(1) Tumours of calices, renal pelvis and ureter.
(2) Ureteropelvic junction obstructive anomalies.

The mornings of 12 and 13 March will be devoted to televised operations. The afternoons of these 2 days and the morning of 14 March will be devoted to communications. Each speaker will have 30 minutes at his disposal and the lectures will be published as monographs by Masson.

Further information from: Secrétariat des Journées Urologiques de Necker, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

Second Congress of the International Society of Urologic Endoscopy

Bristol. 9-11 September 1981.

Those wishing to join the Society should contact the Honorary Secretary, Dr Jorge Morera, Federico Lacroze 2154, (1426) Buenos Aires, Argentina.

Those interested in attending the meeting should contact Miss Sarah Storie-Pugh, Conference Services Ltd, 3 Bute Street, London SW7 3EY.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E Newsam, Western General Hospital, Edinburgh EH4 2XU

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Book Reviews

Strauss and Welt's Diseases of the Kidney. Edited by L. E. Earley and C. W. Gottschalk. Third edition. Volume 1: pp. xvi + 813 + index. Volume 2: pp. vi + 1661 + index. Boston: Little, Brown & Co., 1979. Price $42.50 (each volume).

In 1963, the appearance of "Strauss and Welt" coincided with the emergence of nephrology as a new speciality. Since then the growth and development of the subject have been reflected in this major text. The third edition comes 5 years after the death of both founder editors and is not merely an update of the second edition but also a full revision by mostly a new group of authors. Thus these 2 volumes are in keeping with the changes of the past decade and form a fully comprehensive text, essential for a nephrologist but also full of information for a urologist.

Urology in Practice. Edited by C. J. Devine, Jun. and J. F. Stecker, Jun. Pp. 998. Boston: Little, Brown & Co., 1978. Price $48.50.

The book is written by the 2 editors and 79 contributing authors, amongst whom are some of the best known names in American urology. The contributing authors were asked to write on topics in which they had a special interest, providing the basic information needed by trainee urologists at Senior Resident level and explaining how they themselves used the information to reach decisions. The book includes the principles but not the details of operations but is otherwise comprehensive and profusely illustrated with high quality X-ray reproductions and diagrams. Adequate references, up to 1976, are given at the end of each chapter.

The book is therefore a postgraduate textbook of urology and compares favourably with the others.

Handbook of Urological Endoscopy. J. G. Gow and H. H. Hopkins, with contributions by D. M. Wallace and A. G. England. Pp. 89. Edinburgh: Churchill Livingstone, 1978. Price £13.00.

The book describes recent advances in optical techniques, especially those made by Professor Hopkins; it explains how these advances have transformed urological endoscopic techniques, including photography, which is superbly illustrated in the last 30 pages of the book by coloured photographs of the normal and the abnormal bladder, urethra and prostate. Little urological knowledge is needed to appreciate the high quality of the photographs or understand the text accompanying them and those pages, together with the chapters on the sterilisation of instruments, diathermy and the history of the cystoscope, should be of interest to all those involved in endoscopic work, including nurses. The chapters on the optics of cystoscopes and teaching attachments and their lighting systems (written by Professor Hopkins himself) require a fair bit of physical knowledge but should be read by trainee urological surgeons.

This book should be available in Urological Endoscopic Theatres as all who work in them will find something of interest and value in it.

The Immunopathology of the Kidney. (Current Topics in Immunology Series No. 11.) B. Albini, J. R. Brentjens and G. A. Andres. Pp. 198. London: Edward Arnold, 1979. Price £10.75.

This book, which is intended for nephrologists, researchers and students who are interested in the immunological aspects of renal disease, attempts to bridge the gap between a simple textbook of immunology and complex review articles. This is not an easy task but the authors have, on the whole, achieved their aim, producing a concise textbook which is a very valuable reference source.

The chapters on historical review, basic pathogenic mechanisms, the immunopathology of experimental and spontaneous renal diseases in animals, and the immunopathology of renal disease in man, are excellent and contain a vast amount of detailed information. The concise form of presentation, however, must make it difficult reading for the student without prior knowledge of the subject. The chapter on selected diagnostic procedures is disappointing, particularly since there is no discussion of the problems in interpreting results of immune complex assays in clinical practice. Similarly, the chapter on therapeutic approaches is so brief as to be of little value. With these reservations, this book is to be recommended as a very useful reference source for the clinical nephrologist.

Genitourinary Ultrasonography. Clinics in Diagnostic Ultrasound. Volume 2. Edited by A. T. Rosenfield. Pp. viii + 263. Edinburgh: Churchill Livingstone, 1979. Price £10.00.

While no one would deny that conventional radiology continues to be the mainstay of imaging in the urinary tract, there is no doubt that newer modalities are rapidly extending diagnostic scope and potential. Nuclear medicine is now firmly established in its ability to assess function, while ultrasound and C.T. provide unique methods of studying morphology.

This second volume in the series—Clinics in Diagnostic Ultrasound—provides a comprehensive account of the potential of this non-invasive modality in the diagnosis and management of diseases of the genitourinary tract in the context of other available imaging techniques. The preliminary chapter dealing with current technology and a minimum of simple physics is followed by an overview of the present position of ultrasound and C.T. in the management of renal masses. Chapters on percutaneous nephrostomy, renal transplantation and evaluation of the non-functioning kidney are followed by sections devoted to diseases of the prostate and bladder. A chapter is rightly reserved for the increasingly important roles of isotopes and ultrasound in neonatal urology.

Two-thirds of the 260 pages are thus devoted to urology and while the latter part covering gynaecology may be of passing interest to the urologist, it may perhaps have been better incorporated into the next volume dealing with obstetrics. The pages at the end of the book devoted to individual case studies add little to the overall value of the book.

There is a great deal of relevant information in this short book and its concise nature makes it easy to read. The text is complemented by many good quality grey scale pictures and references are extensive and up-to-date. Anyone involved in the practice of urology who is prepared to spend a few hours reading it will at the end have acquired a good working insight into what ultrasound has to offer at the present time. Accepting that diagnostic imaging is moving ahead rapidly and texts soon become dated, at its price this book represents excellent value in presenting the current state of the art and would certainly not go amiss in a departmental library.

Care of the Patient with Neurogenic Bladder. S. Boyarsky, P. Labay, P. Hanick, A. Abramson and R. Boyarsky. Pp. 250. Boston: Little, Brown and Company, 1979. Price $13.50.

It is accepted nowadays that paraplegics should be cared for in a special centre by a consultant with a team of specialists at hand and close support from trained nurses and rehabilitationists. As the patient's future health and life expectancy depend to a large extent on the fate of his urinary tracts, urological care must have a high priority. This is the message which this valuable handbook carries and it is comprehensive to a fault, with a particularly welcome chapter on sexual problems which have often been neglected in the past.

Unfortunately, the theme of the book is often obscured by conceptual embellishments, unnecessary academic details and a tendency towards obscure wording and turgid phraseology. Vesicourethral pathophysiology may be complex but this is no reason to abandon attempts at classification altogether. Judicious over-simplification is essential in a practical manual like this if readers are to understand what they are expected to do for the patient. The illustrations do little to help. Most of them are taken from other works and many look like poor photocopies. They often appear irrelevant to the text (*e.g.* Figs. 2.12, 8.15 and 16) and some are wrongly referred to (*e.g.* Fig. 6.2). Figure 8.1 is upside down and in Figure 2.17 afferent and efferent pathways are wrongly labelled. A future edition would be greatly improved by attention to these points and by avoiding repetition of material in several chapters. Certain sections could be left out altogether, such as those on the general properties of antibiotics, the physical examination of the abdomen and various cystometric tracings, though these do deny the muscular contractions attributed to the lower motor neurone bladder on pages 26 and 91. Misprints are fortunately few, but urethra and ureter are confused on page 179 and twice on page 109.

On the other hand, reference should have been made to the vital role of the anal and bulbocavernosus reflexes in the prognosis for reflex bladder function, and to Glahn's work on the optimum stimulus for bladder contraction (this is incorrectly described under Fig. 5.2 and omitted from the text altogether). Some indication of an acceptable level of residual urine should have been given—surely this is any volume compatible with sterility and continued radiological normality of the upper urinary tracts. Finally, the modern science of urodynamics is omitted from the index and given but a single line in the text. Further attention to this subject would enable precise indications to be given for various medical and surgical procedures instead of the many vague and often old-fashioned suggestions.

Nephrology. Edited by J. Hamburger, J. Crosnier and J.-P. Grünfeld. Second edition. Pp. xvi + 1393. Chichester: John Wiley, 1979. Price £42.50.

The second edition of *Nephrology* is a very complete textbook of both paediatric and adult renal medicine. Over 100 authors, drawn from all over the world, are involved, and it does not therefore present the same cohesive view of nephrology as the original edition, which was entirely written and edited by the staff at the Necker Hospital. Indeed, on several points the authors of different chapters disagree. Perhaps this is good, because nephrology is full of controversy and it is as well that the general reader is aware of this. However, strong editing by Professor Hamburger and his colleagues has ensured a certain uniformity of approach, which is the main strength of this textbook.

The section on Anatomy, Embryology and Physiology is admirably written and concise, with clear drawings and micrographs. "Exploration of the Kidney and

Major Syndromes" has good sections on the investigation of renal disease and the interpretation of urinary findings and commonly used laboratory tests. It also has excellent chapters on hypertension and chronic renal failure, which are given a very full and well referenced treatment. The heart of the book is the section on Renal Diseases, particularly those chapters devoted to glomerulonephritis and renal involvement in systemic diseases. These admirably reflect trends in nephrology in recent years and are warmly recommended to anyone who wishes to understand more about these fascinating disorders.

"Congenital and Hereditary Diseases" of the kidney are covered in a descriptive fashion. Urinary tract stones, renal vein thrombosis, tuberculosis and pregnancy are included under this general heading. The final part is on "Treatment". The reader looking for advice on how to treat specific renal diseases will be disappointed, since most of this section is devoted to consideration of chronic haemodialysis and transplantation. This reflects nephrology as it is practised; specific forms of treatment for the majority of renal diseases are unusual or largely experimental, and are briefly mentioned alongside the description of the diseases themselves.

In summary, this is an interesting and very readable textbook which presents a view of nephrology as it is practised and as it reflects the research efforts of nephrologists.

Prostate Gland and Seminal Vesicles. Handbuch der mikroskopischen Anatomie des Menschen, Volume 7, Part 6. G. Aumuller. Pp. 380, profusely illustrated. Berlin: Springer-Verlag, 1979. Price DM 280; US $154.

The author of this book has aimed to close the information gap that has developed between biochemical and morphological analysis in the field of the male accessory sex glands. He largely (but not entirely) succeeds.

This is a valuable source of reference for the researcher and for the clinician with a special interest in the prostate and seminal vesicles, since all basic information can be found either within the book or through the comprehensive and up-to-date references. It is well produced and the illustrations are of the highest quality. There is an orderly and logical subdivision of the text into concise chapters and subheadings, and the text itself is easy to read despite the voluminous references.

The author brings together a great deal of material culled from work by morphologists, morbid anatomists, biochemists and endocrinologists, and particularly noteworthy is the large amount of original material contributed by the author himself, who is a cell biologist. In the early part of the book reference is made to the embryology and anatomy of the prostate gland and seminal vesicles, and there is a welcome introduction to the morphology of the functional prostate proposed by McNeal. This raised the hope that subsequent chapters would deal with the histochemistry and ultrastructure of the human gland on this basis, but the author's failure to do so merely reflects the fact that this work remains to be done.

Apart from the researcher with an interest in the accessory sex glands and their function, the more general reader will find this a stimulating book which contains much new and provocative information.

A book as comprehensive and well produced as this is inevitably highly priced, but this in no way detracts from its intrinsic value.

Urologic Endoscopic Procedures. Alice Morel and G. J. Wise. Second edition. Pp. 223 + xiii; 258 illustrations. St Louis, Toronto, London: The C.V. Mosby Co., 1979. Price £11.25. (London: Year Book Medical Publishers.)

This book fulfils its purpose of providing students, technicians and graduates learning urology with basic information about urological endoscopic procedures and instruments, sterilisation techniques and urodynamics. Although the volume highlights the newest endoscopic equipment, it retains many illustrations of instruments lit by incandescent bulbs. Surely these instruments should be excluded from this edition, since the few who still use them could obtain all the information needed from the first edition published in 1974.

Books Received

L'Investigation Vasculaire par Ultrasonographie Doppler. C. Cranceschi. Second edition. Pp. 106. Paris: Masson. 1979.

Pyelonephritis. F. Renyi-Vamos and F. Balogh. Pp. 191. Budapest: Akademiai Kiado. 1979. Price $16.50.

Physiological Basis of Diuretic Therapy. L. I. Juncos. Springfield: C. C. Thomas. 1979. Price $10.75.

Progress in Glomerulonephritis. Edited by P. Kincaid-Smith, A. J. F. d'Apice and R. C. Atkins. Pp. x + 458. Chichester: Wiley and Sons Ltd, 1979. Price £27.50.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which the papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal. A general section is included at the end.

ADRENAL

Disorders of the adrenal. [8 papers.] (H. Bricaire *et al.*) *Rev. Prat.* 1979, **29**, 3233.

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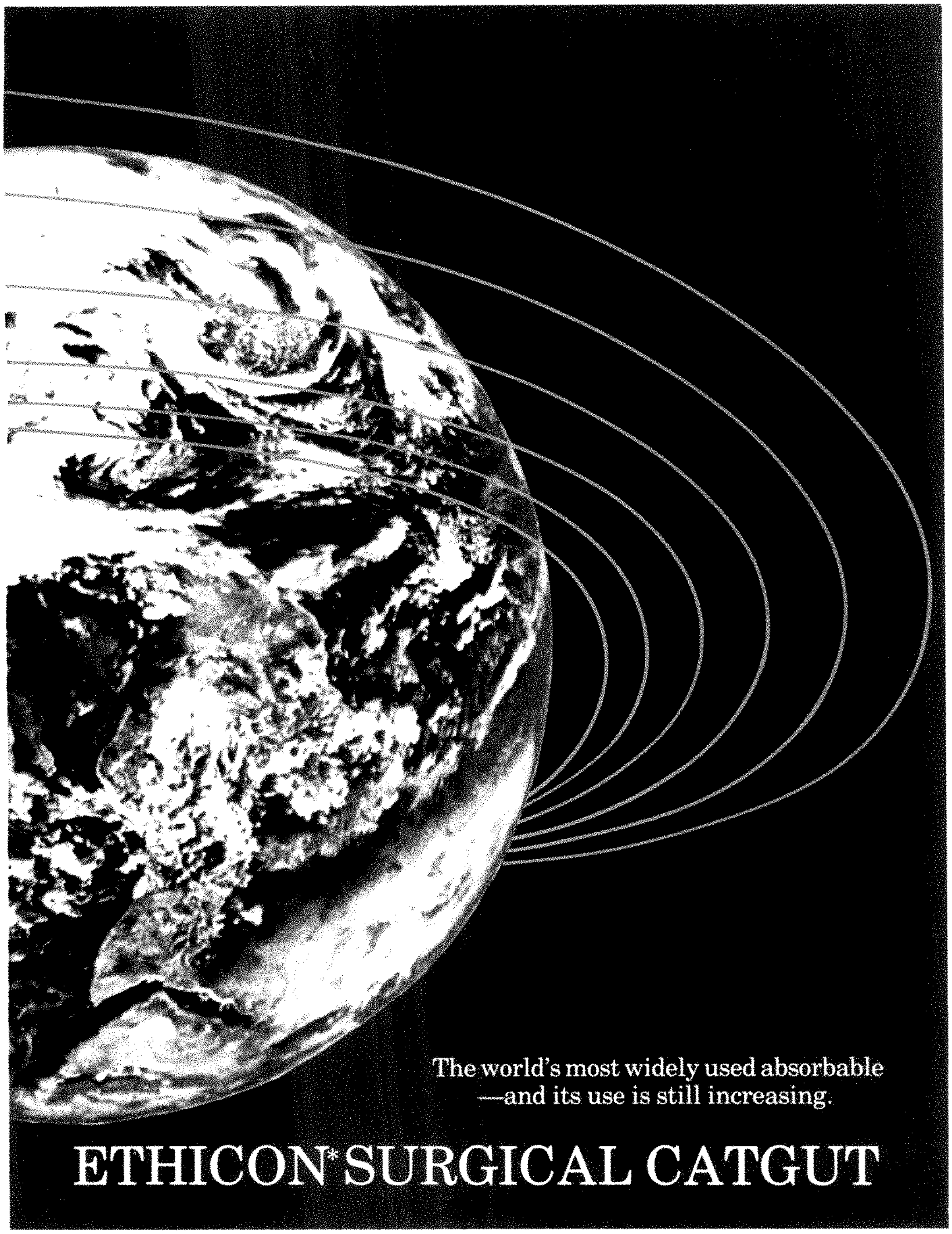
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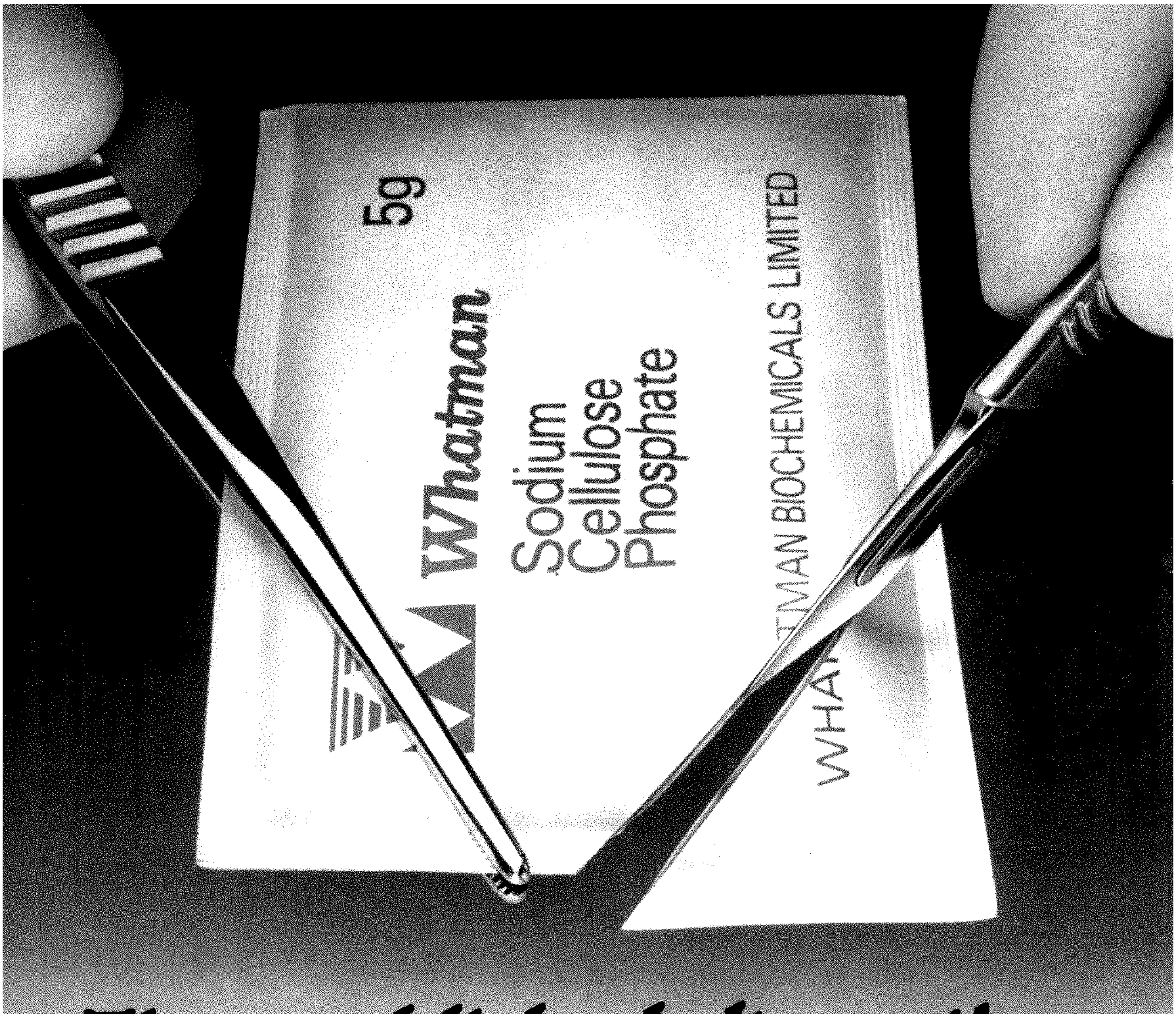

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Indications: Bronchitis, Sinusitis, Prostatitis, Salpingitis and other infections caused by susceptible strains of Gram-positive and Gram-negative organisms including some tetracycline-resistant strains of Staphylococci.
Dosage: Adults only – 2 tablets initially followed by one tablet b.d. **Contra-indications:** Known hypersensitivity to tetracyclines; systemic lupus erythematosus. **Precautions:** Use with caution in patients with hepatic or severe renal dysfunction; absorption of MINOCIN is impaired by concomitant administration of preparations containing calcium, magnesium or aluminium but not by food or milk in moderate quantities. **Warnings:** The use of MINOCIN may occasionally result in overgrowth of resistant organisms and, during tooth development may cause discolouration of teeth. **Side-effects:** Nausea, vomiting and occasionally dizziness. **Legal category:** P.O.M.
Package quantities: Packs of 9 and 45 tablets. Code 5334. **Basic NHS Price:** Tablets 100mg, 9, £3.23; 45, £15.78.
Date of preparation or last review: June, 1979.

Full prescribing information is available on request.

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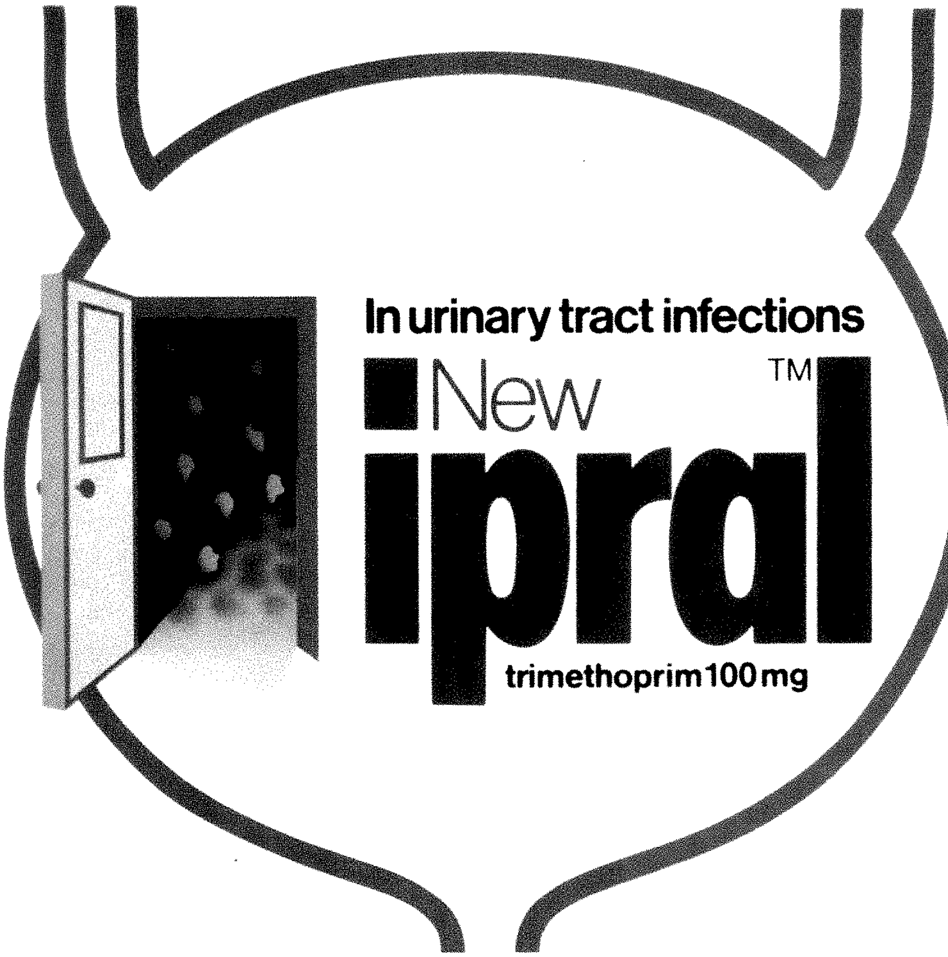

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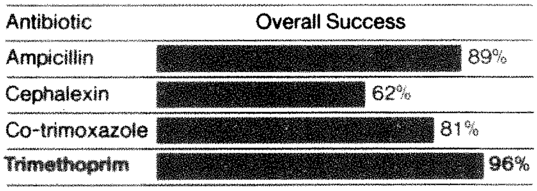

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Antibiotic	No. of Patients	% Side Effects
Ampicillin	88	22
Cephalexin	84	25
Co-trimoxazole	83	21
Trimethoprim	**84**	**8**
Total	339	

Prescribing information

IPRAL tablets

Each tablet contains trimethoprim B.P. 100 mg.

Indications

Ipral is indicated for the treatment and prophylaxis of acute and chronic urinary tract infections.

Actions

Ipral is active in-vitro against most pathogenic Gram-positive and Gram-negative bacteria. Exceptions include Neisseria species and Pseudomonas aeruginosa.

Dosage and administration

For acute urinary tract infections 2 tablets twice daily is recommended. For long term and prophylactic therapy 1 tablet twice daily is recommended.

Contra-indications

Ipral should not be given to patients with severe renal insufficiency where blood levels cannot be monitored regularly. Ipral should not be used in pregnancy or during the first few weeks of life.

Precautions

Care is necessary in administration to patients with impaired renal function. Special precaution should be exercised in patients with a predisposition to folate deficiency.

Side-effects

Nausea, vomiting and skin rashes may occur but are rare. Ipral may depress haematopoiesis during prolonged therapy. This has proved reversible when treated with calcium folinate.

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- Avoids the side effects of sulphonamides
- At a sensible price

and "Trimethoprim given alone was shown to be much better tolerated."[2]

"Treatment with T.M.P. (trimethoprim) alone is superior to the combined regimen due to a smaller incidence of side-effects; ..." thus "... introduction of T.M.P. alone on the market is recommended."[4]

"Less gastrointestinal side-effects and skin rashes have occurred with trimethoprim ..."[3]

References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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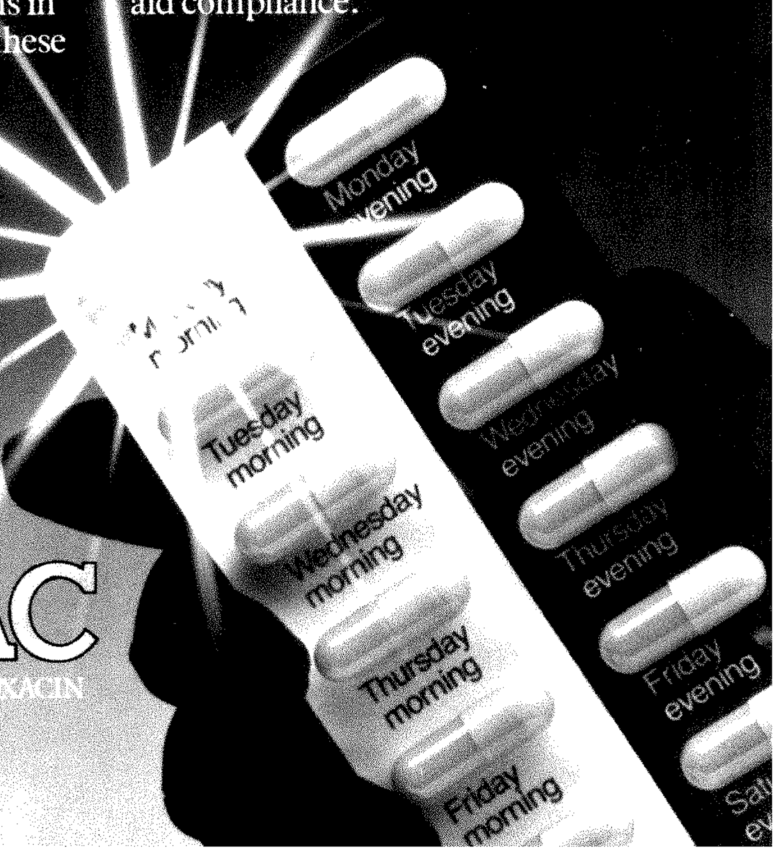

CINOBAC

CINOXACIN

Prescribing Information

"CINOBAC" Cinoxacin INN

Presentation

Capsules containing 500 mg cinoxacin INN PC.

Uses

CINOBAC is indicated in acute, recurrent and chronic upper and lower urinary tract infections due to susceptible micro-organisms.

Dosage & Administration

CINOBAC is administered orally. The usual adult dose is 1 g daily in two divided doses.

Contra-indications

Cinoxacin is contra-indicated in patients with a history of hypersensitivity to cinoxacin.

Warnings

The use of cinoxacin is not recommended during pregnancy, for the nursing mother, or for children as safety has not been established.

Precautions

CINOBAC is not recommended for patients with severely impaired renal function and should be used with caution in patients with reduced renal function.

Adverse Reactions

Gastro-intestinal – nausea, anorexia, vomiting, abdominal cramps and diarrhoea have been reported.

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Other adverse reactions possibly related to cinoxacin include dizziness, headache, insomnia, tingling sensation, perineal burning, photophobia and tinnitus.

Transient changes in AST (SGOT), ALT (SGPT), BUN, ALP and creatinine clearance have been observed occasionally.

Product licence

PL 0006/0124

Price

Basic NHS price ex calendar pack 79p per day.

References

1. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), II, 1041. American Society for Microbiology, 1978.
2. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), I, 704. American Society for Microbiology, 1978.
3. Proceedings of the 9th International Chemotherapy Congress, 1976, 5: 417.
4. Antimicrobial Agents and Chemotherapy, 1976, 9: 502.

*Including patients with physical abnormalities of the urinary tract.

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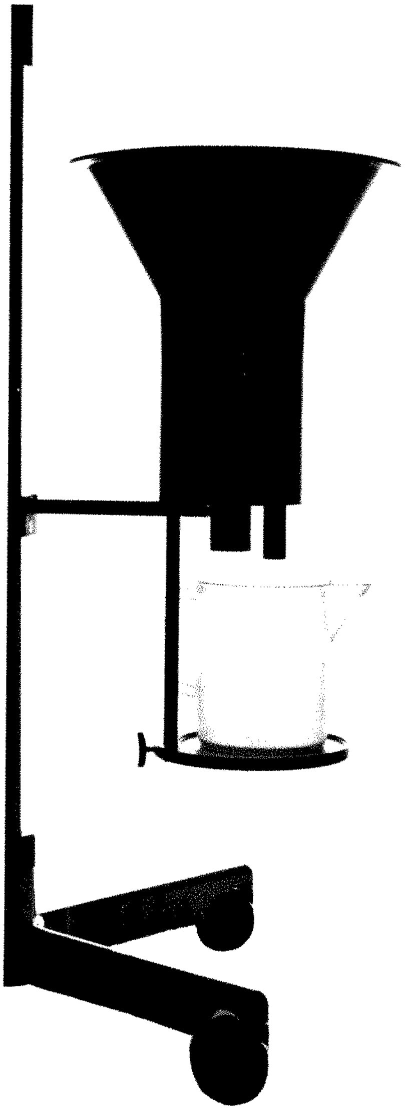

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sulphate equivalent to
ikacin activity 500mg. The
contains methyl and propyl
ben. AMIKIN PAEDIATRIC
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contains in 2ml, amikacin
sulphate equivalent to
ikacin activity 100mg. The
ampoule contains no
eservatives. **Uses** AMIKIN
ikacin sulphate) is a semi-
synthetic aminoglycoside
antibiotic which is active
gainst a broad spectrum of
Gram-negative organisms,
cluding Pseudomonas and
some Gram-positive
organisms.
osage and Administration
*amuscular or intravenous
administration* For most
fections the intramuscular
ute is preferred, but in life-
reatening infections, or in
patients in whom
ramuscular injection is not
feasible, the intravenous
route, either slow bolus
(2-3 minutes) or infusion
(30 minutes) may be used.
ts and children 15mg/kg/
day in two equally divided
ses. Use of the 100mg/2ml
ength is recommended for
children for the accurate
measurement of the
ppropriate dose. *Neonates
and premature infants* An
al loading dose of 10mg/kg
ed by 15mg/kg/day in two
equally divided doses. *Life
eatening infections and/or
e caused by pseudomonas*
The adult dose may be
ased to 500mg every eight
hours but should neither
exceed 1.5g/day or be
administered for a period
longer than 10 days. A
aximum total adult dose of
g should not be exceeded.
Impaired renal function In
tients with impaired renal
tion, the daily dose should
duced and/or the intervals
etween doses increased to
accumulation of the drug.
*tra-indications, warnings,
tc* Patients should be well
hydrated during AMIKIN
therapy. In patients with
impaired renal function or
diminished glomerular
ltration, AMIKIN should be
used cautiously. In such
ents, renal function should
be assessed by the usual
thods prior to therapy and
odically during therapy. As
ith other aminoglycosides,
ototoxicity and/or
hrotoxicity can result from
se of AMIKIN, precautions
on dosage and adequate
ration should be observed.
use of AMIKIN in patients
with a history of allergy to
noglycosides or in patients
may have subclinical renal
or eighth nerve damage
ed by prior administration
ephrotoxic and/or ototoxic
ents should be considered
caution, as toxicity may be
additive. In these patients
MIKIN should be used only
if, in the opinion of the
physician, therapeutic
advantages outweigh the
potential risks. The risk of
otoxicity is increased when
IKIN is used in conjunction
with rapidly acting diuretic
ugs, particularly when the
diuretic is administered
ntravenously. Such agents
include frusemide and
acrynic acid, which is itself
otoxic agent. Irreversible
deafness may result.
Pregnancy: The safety of
IKIN in pregnancy has not
yet been established. **Side
effects**: When the
mmended precautions and
dosages are followed the
cidence of toxic reactions,
ch as tinnitus, vertigo, and
partial reversible or
irreversible deafness, skin
ash, drug fever, headache,
paraesthesia, nausea and
ting is low. Urinary signs of
irritation (albumin, casts,
and red or white cells),
zotaemia and oliguria have
reported. AMIKIN should
ot be physically mixed with
her antibacterial agents in
ges, infusion bottles or any
her equipment. Each agent
should be administered
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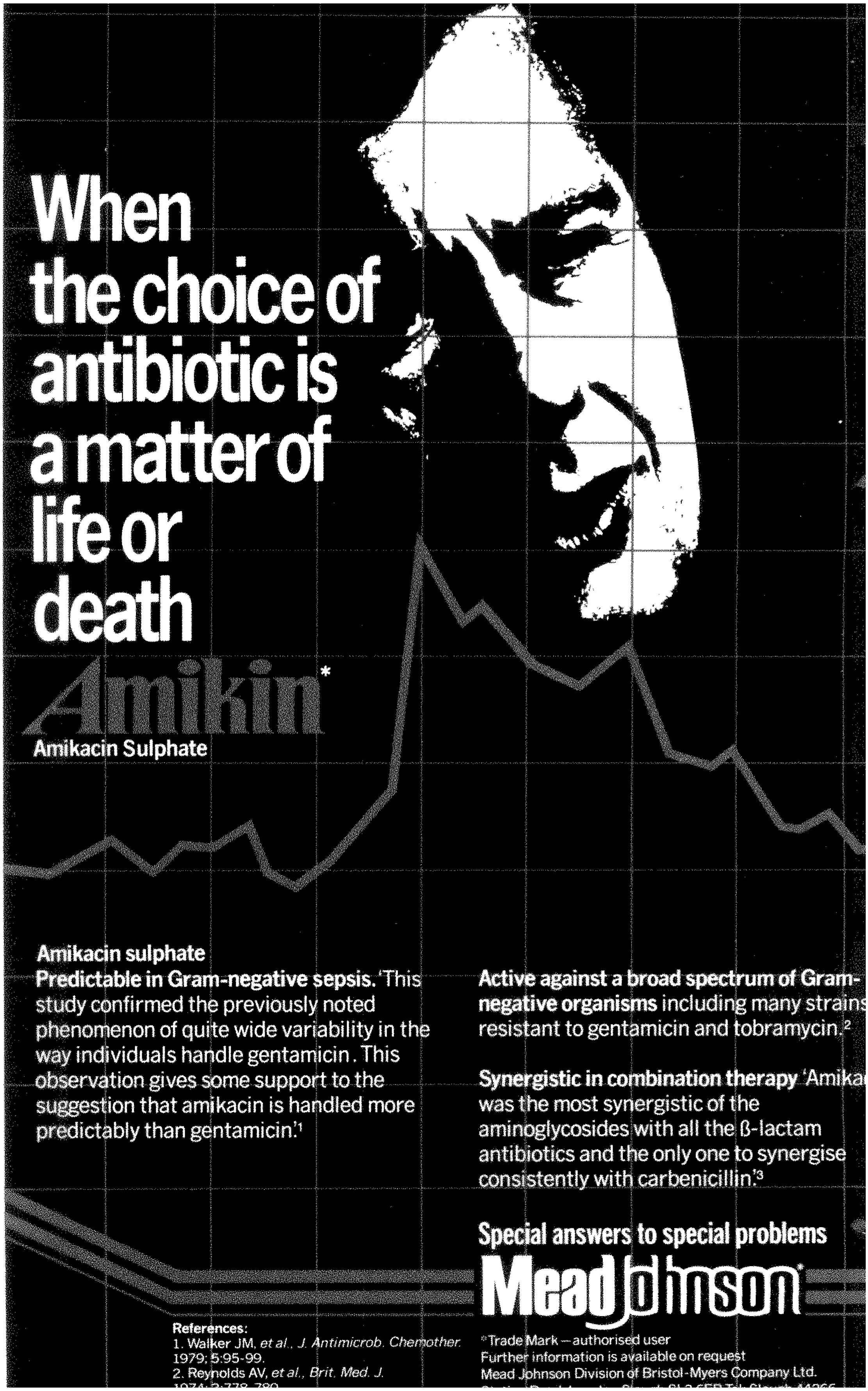

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2. Reynolds AV, *et al., Brit. Med. J.*

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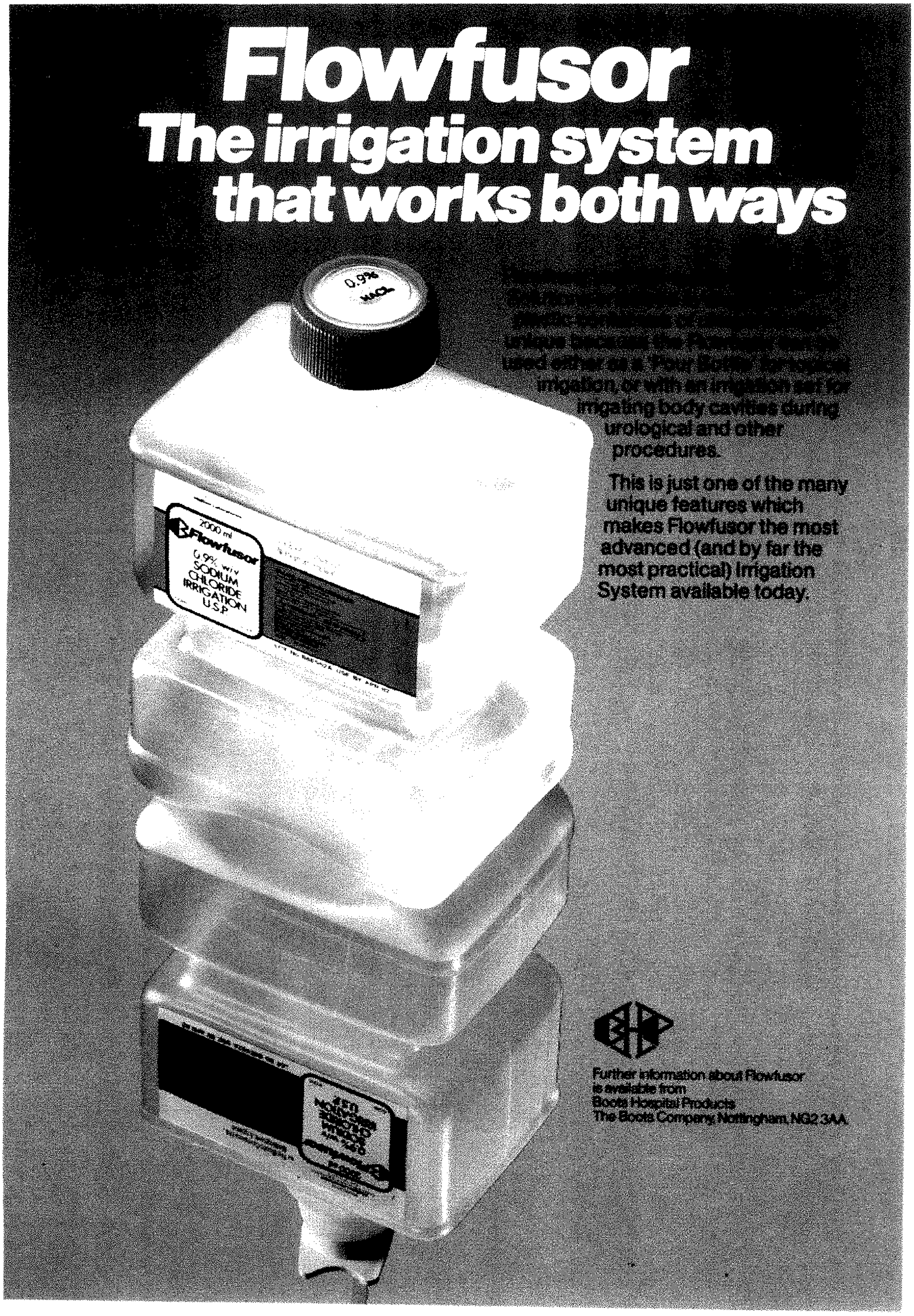

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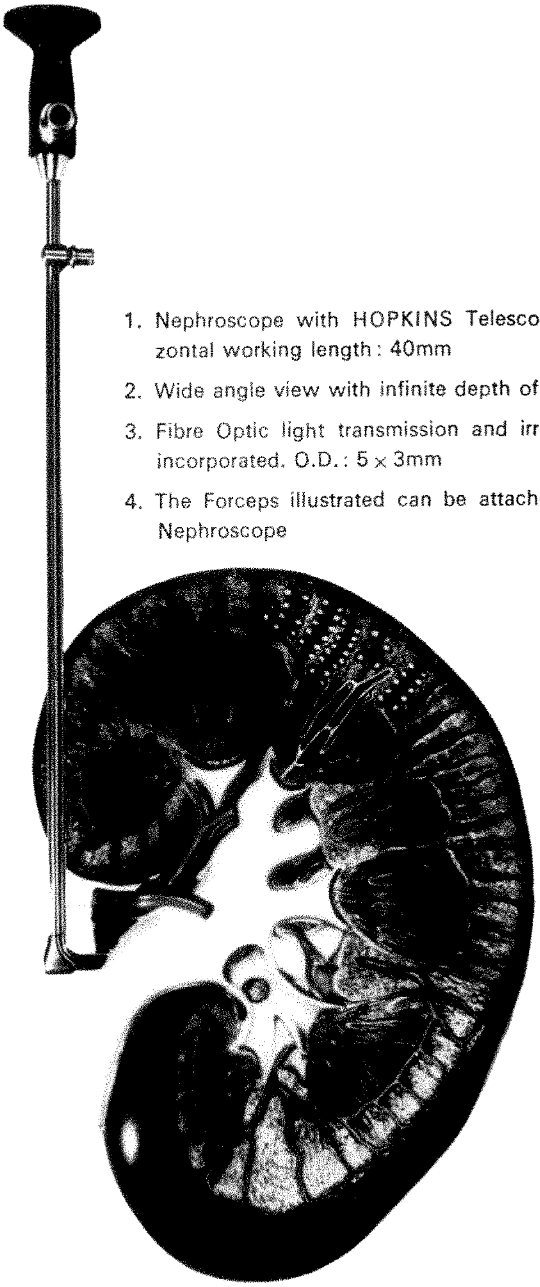

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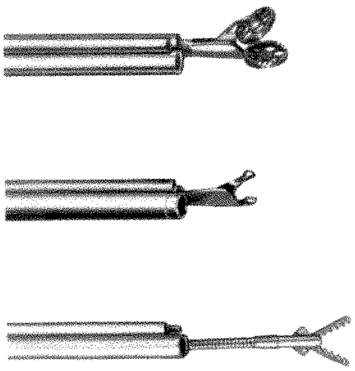

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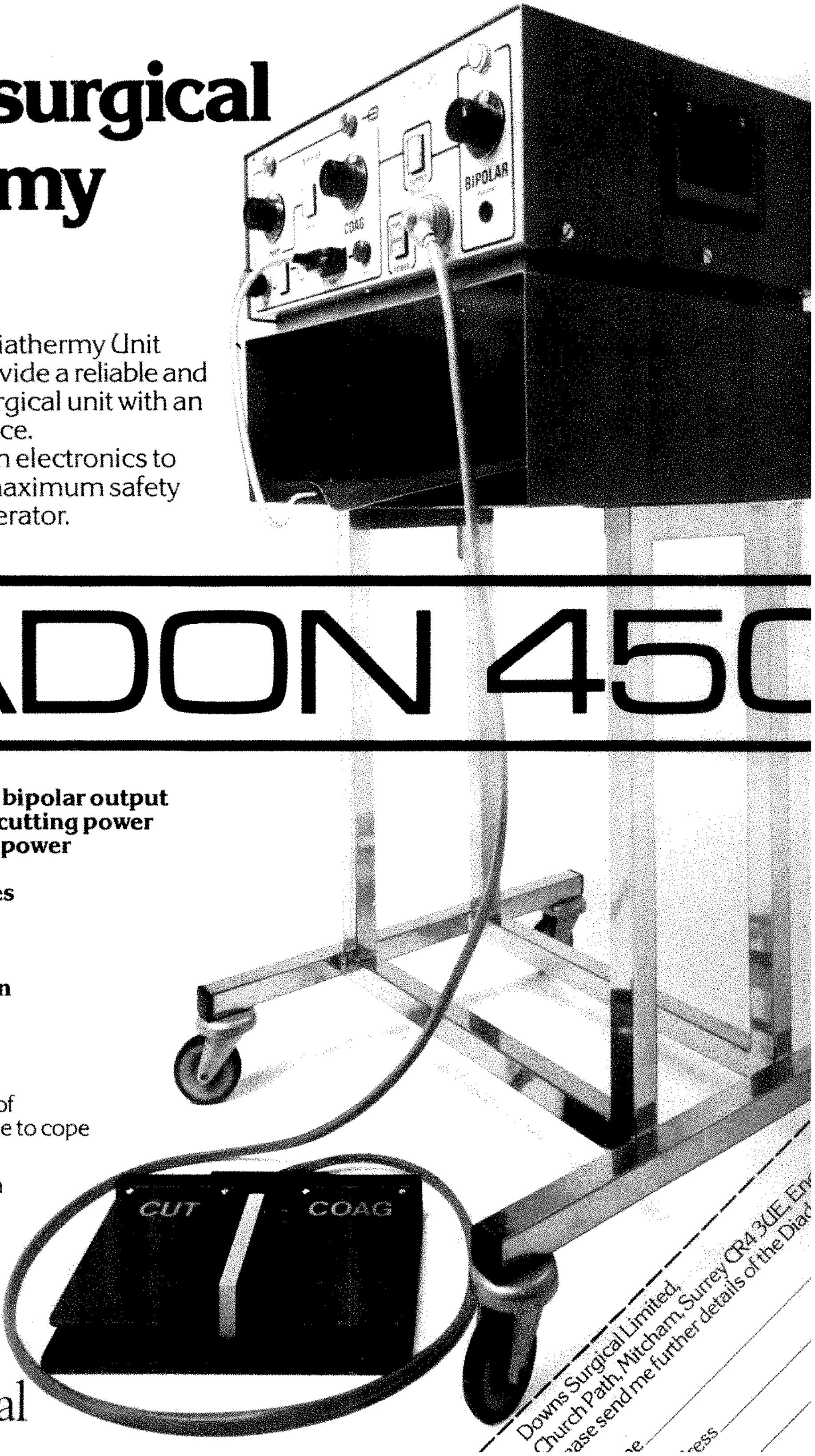

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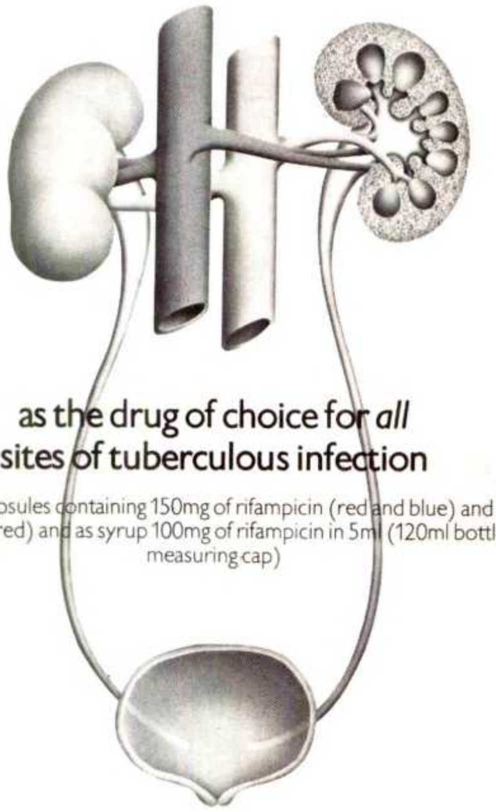

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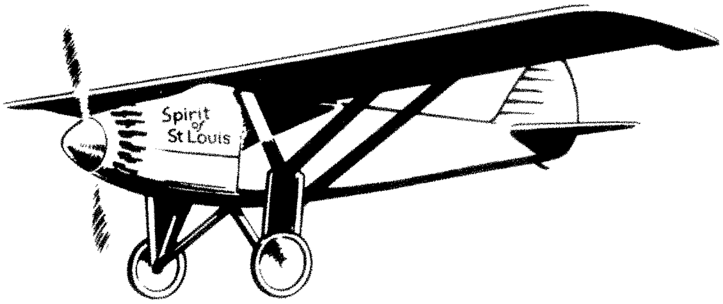

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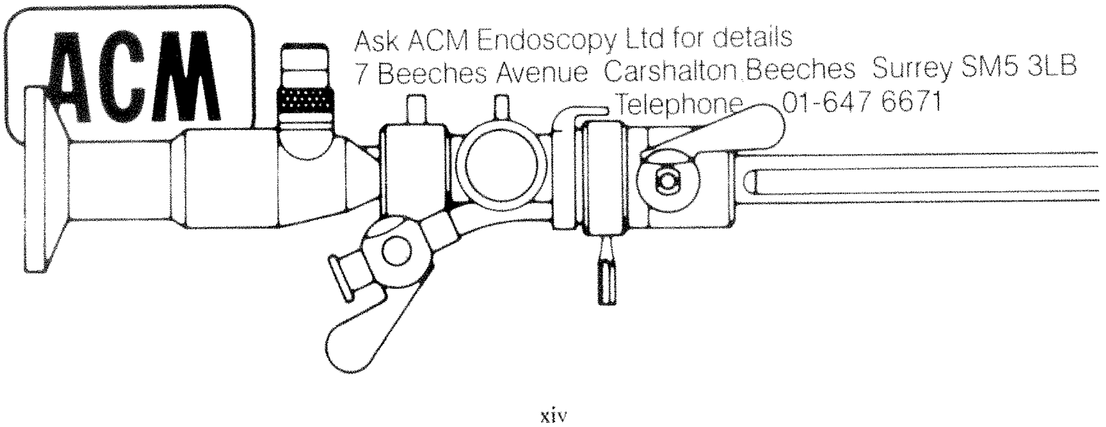

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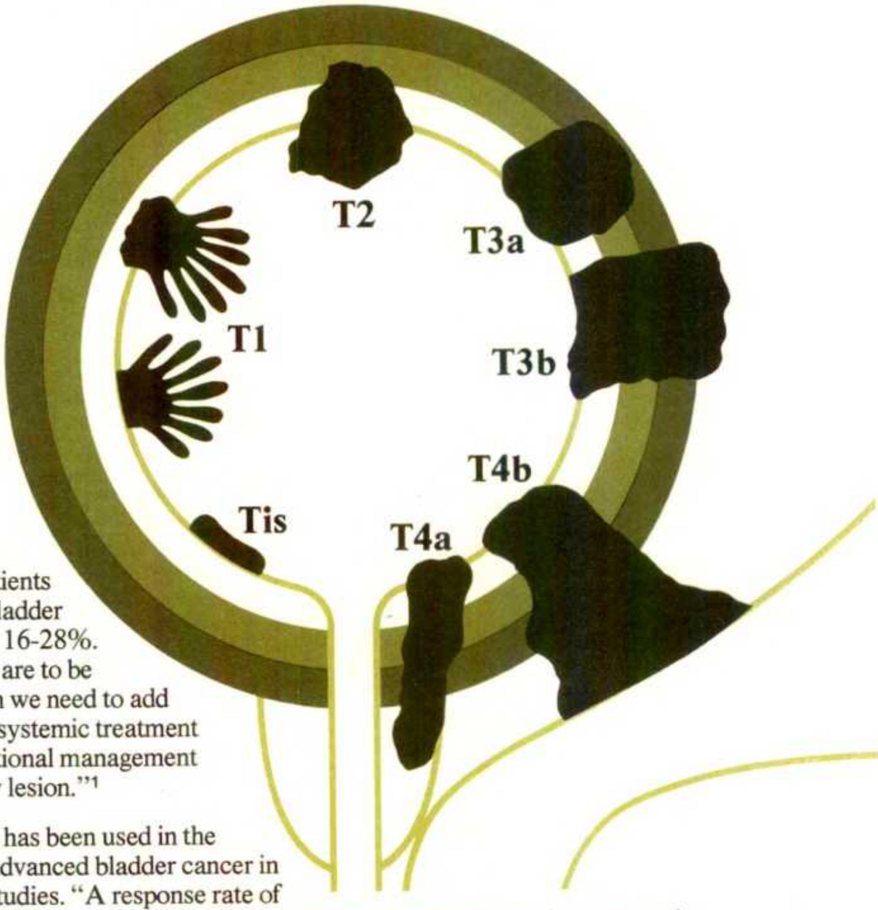
Methotrexate in advanced bladder cancer



The 5-year survival of patients with T2/T3 bladder cancer is only 16-28%. "If the results are to be improved then we need to add some form of systemic treatment to the conventional management of the primary lesion."[1]

Methotrexate has been used in the treatment of advanced bladder cancer in a number of studies. "A response rate of 56% was found in patients who received 100 mg of methotrexate intravenously every 2 weeks as an out-patient."[2] These authors concluded that "Methotrexate is a well-tolerated chemotherapeutic agent with few of the more unpleasant side-effects noted with other agents."[2]

"In view of the promising results . . . it is surprising that methotrexate has not been more widely used in the treatment of bladder cancer."[3]

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1. *Brit. med. J. 1977, 2, 1562*
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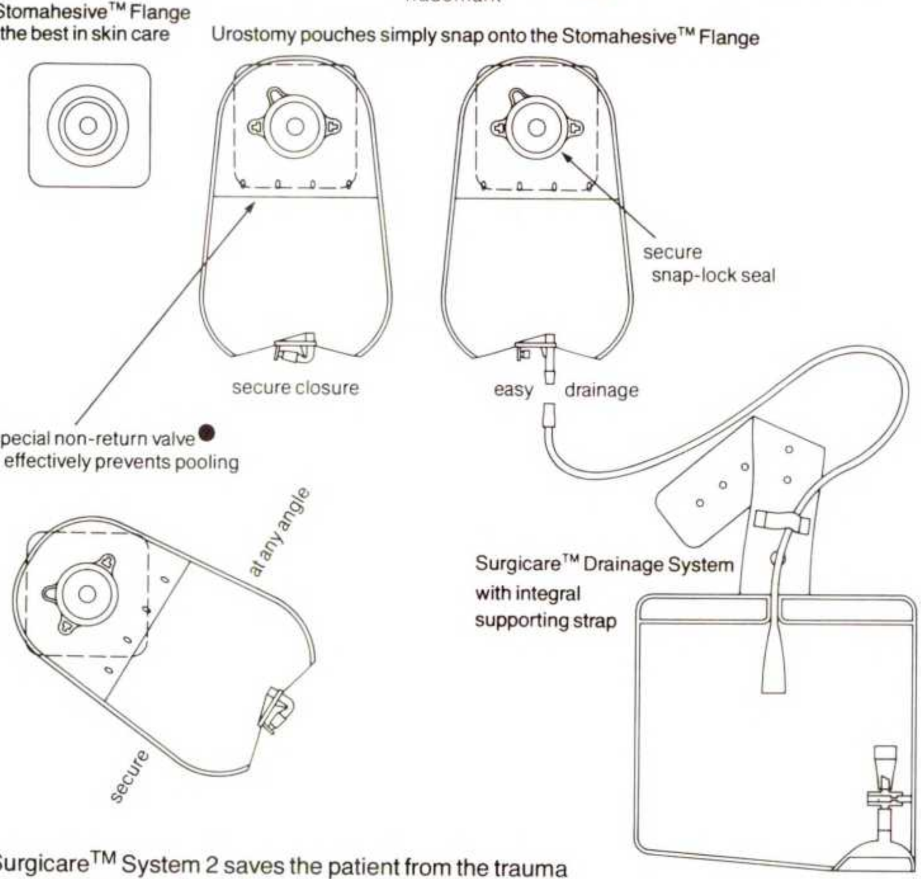
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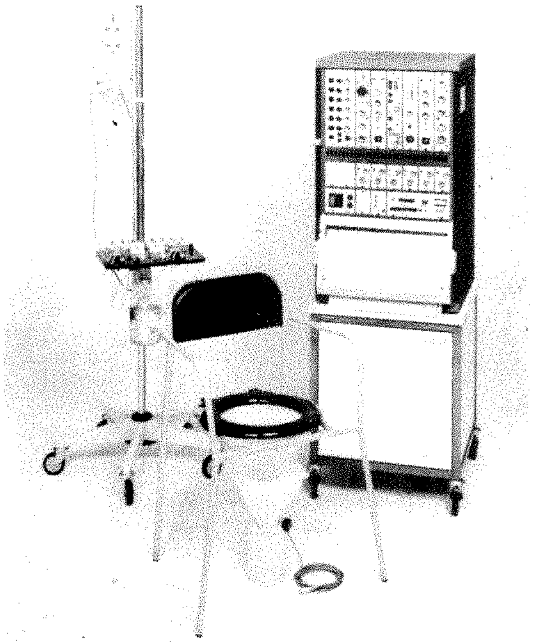

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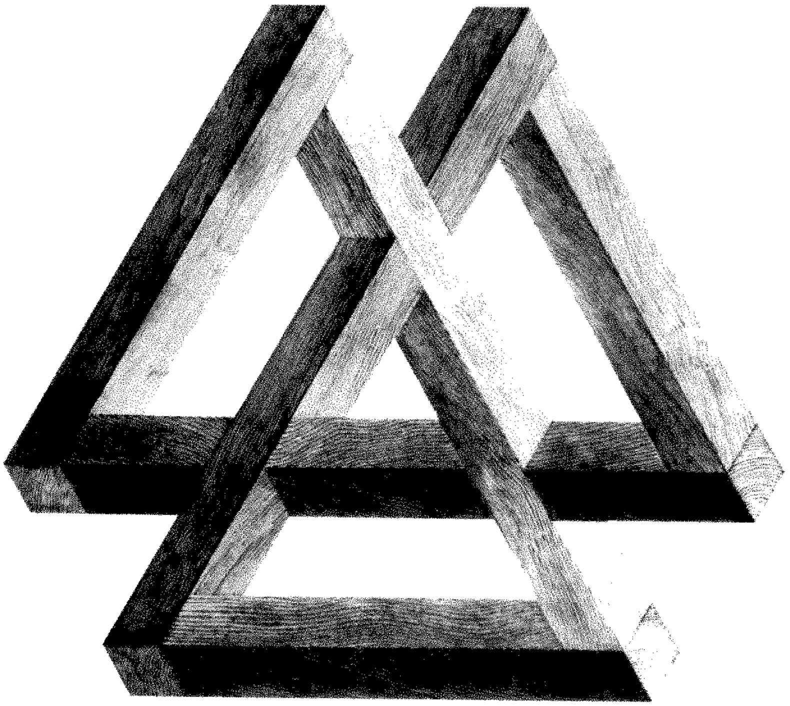

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Nephrostomy in Cancer Patients: To Do or Not To Do?

B. FALLON, L. OLNEY and D. A. CULP

Department of Urology, The University of Iowa Hospitals and Clinics, Iowa City, USA

Summary—One hundred patients who have had nephrostomies performed for obstructive uropathy in the presence of extensive carcinoma have been retrospectively analysed. Patients with prostatic and cervical carcinoma had a moderately good long-term survival and quality of life, but those with bladder carcinoma or other primary sites had poor results. Significant factors in the selection of patients for nephrostomy drainage in the presence of pelvic cancer are discussed.

When ureteric or ureteropelvic obstruction is present in a patient secondary to benign disease, the question sometimes arises as to whether a nephrostomy should be performed and whether it should precede or be concurrent with the definitive reconstructive procedure. In patients with malignant disease, the question most often is whether a nephrostomy or any urinary diversion should be performed at all. Philosophical, ethical and emotional issues often cloud medical judgement. In some institutions, committees have been formed to aid in the decision to divert or not. Most often, the discussion is held between the urologist and patient or family, and it would seem advisable to have as much information at hand as possible in informing the patient and family of the likely consequences of nephrostomy. We report our experience with this problem.

Materials and Methods

From 1966 to 1976, a total of 378 patients had unilateral or bilateral nephrostomies performed at our institution. On reviewing their charts, it was found that 100 of these patients had a diagnosis of upper urinary tract obstruction associated with invasive, incurable cancer. Sixty-five of these were male, 35 were female. Ages ranged from 15 to 84 years. The site of the primary malignancy was prostate in 37 patients, bladder in 29, cervix in 15, and miscellaneous in 19 (Table 1).

Table 1 Locations of Primary Tumours

Genitourinary system	
Prostate	37
Bladder	29
Cervix	15
Ovary	4
Vulva	1
Gastrointestinal system	
Colon	7
Pancreas	1
Lymphoma	5
Neuroblastoma	1
Total	100

Seventy-one patients were azotaemic at the time of the nephrostomy (blood urea more than 15 mmol/l). Radiographic evidence of bilateral ureteric obstruction was present in 76 patients, and of unilateral obstruction in 15 patients. Six of these 15 patients had solitary kidneys. One patient had urethral obstruction secondary to carcinoma of the vulva, but normal upper tracts. No pre-operative radiological studies were obtained in 8 patients because of severe azotaemia and hyperkalaemia, which dictated emergency treatment. In 60 cases, unilateral nephrostomy was performed, and in 40 patients, bilateral nephrostomy was done, either simultaneously or sequentially.

In 80 patients, some form of therapy for the primary malignancy had been given at varying intervals prior to the need for a nephrostomy (Table 2).

Results

Two patients were lost to follow-up. Three patients,

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Table 2 Treatment of Neoplasm Before and After Nephrostomy

Neoplasm	*Before nephrostomy*				*After nephrostomy*			
	None	*Surgery*	*Radiation therapy*	*Chemo-therapy including orchiectomy*	*None*	*Surgery*	*Radiation therapy*	*Chemotherapy including orchiectomy*
Cervix	4	4	10	0	5	1	9	2
Prostate	8	11	6	28	14	2	8	22
Bladder	5	23	13	2	15	4	9	4
Misc.	3	10	4	7	7	0	4	9
Total	20	48	33	37	41	7	30	37

one each with lymphoma, carcinoma of the prostate and carcinoma of the cervix are alive. Ninety-five patients are dead.

Operative Complications

No intra-operative deaths occurred. Only 2 patients had problems with intra-operative haemorrhage and hypotension. There were 31 post-operative complications in 27 patients (Table 3). Eighteen patients died in hospital and the average time in hospital, from nephrostomy to death, was 32 days, with 2 patients exceeding 100 days in hospital and 4 others exceeding 40 days.

The average stay for the survivors was 31 days (Table 4), but this is distorted by the fact that some patients were retained for radiation therapy. Fifty-nine patients survived well enough to have some form of therapy directed at their neoplasm (Table 2). Six of these had resolution sufficient to allow removal of the nephrostomy tube, although one of these 6 required diversion later.

Table 3 Post-operative Complications

Infection	
Septicaemia	10
Wound infection	2
Pneumonia	2
Cardiovascular	
Haemorrhage	5
Pulmonary embolus	2
Pulmonary oedema	1
Cardiac arrhythmia	1
Thrombophlebitis	1
Cerebral infarction	1
Gastrointestinal	
Bowel obstruction	3
GI haemorrhage	1
Perforated ulcer	1
Intestinal fistula	1
Total	31

Analysis by Site of Primary Neoplasm

1. Prostate Cancer (Fig. 1). Thirty-seven patients. Average age at nephrostomy: 69.5 years. Average interval between initial diagnosis and nephrostomy: 33.2 months. Average survival from nephrostomy to death: 12.2 months, median 7 months. Average interval between initial diagnosis and death: 45.4 months. There were 7 deaths prior to discharge from hospital. Eighteen of 37 patients survived longer than 6 months. Fourteen survived longer than 12 months. Six survived longer than 24 months. Of 14 patients surviving longer than 12 months, the interval between initial diagnosis and nephrostomy averaged 49.5 months. Of 23 patients surviving less than 12 months, the interval between initial diagnosis and the need for nephrostomy was 23.3 months. There was no difference in the pre-operative blood urea and creatinine levels between those patients who died post-operatively and those who were discharged, or between short-term and long-term survivors. Pre-operative potassium levels, likewise, had no influence on survival.

2. Bladder Cancer (Fig. 2). Twenty-nine patients. Average age at nephrostomy: 67.6 years. Average

Table 4 Post-nephrostomy Mortality and Length of Hospitalisation

Neoplasm	*Number of patients*	*Number of deaths in hospital*	*Survivors' hospital stay (days)*
Cervix	15	2	45
Prostate	37	7	23
Bladder	29	5	36
Misc.	19	4	25
Total	100	18	31

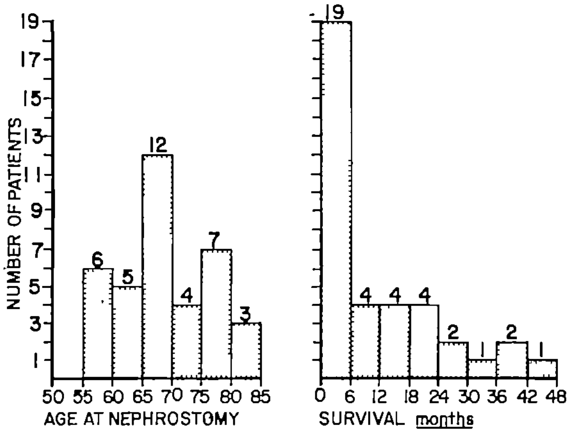

Fig. 1 Nephrostomy in prostatic cancer.

interval between initial diagnosis and nephrostomy: 30.7 months. Average survival following nephrostomy: 4.5 months. Average interval between initial diagnosis and death: 35.2 months. Twenty patients survived for 4 months or less and 5 of these died in hospital without being discharged following nephrostomy. There was no difference in the interval between initial diagnosis and nephrostomy between the short-term and long-term survivors. Likewise, the pre-operative blood urea, creatinine and potassium levels were no different between these groups.

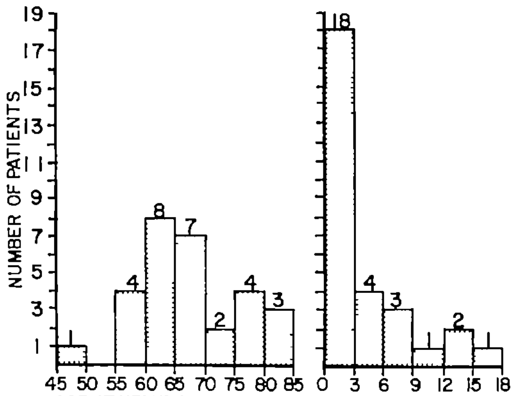

Fig. 2 Nephrostomy in bladder cancer.

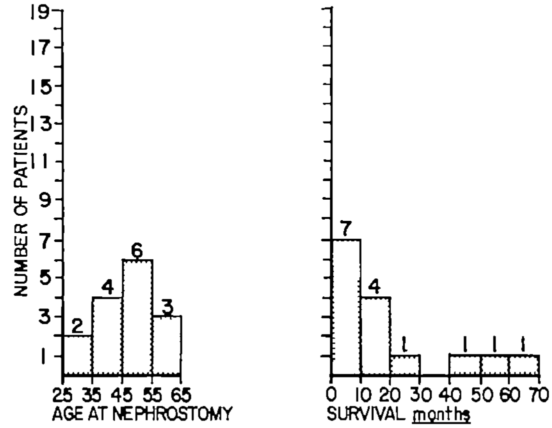

Fig. 3 Nephrostomy in cervical cancer.

3. Cervix (Fig. 3). Fifteen patients. Average age at nephrostomy: 47.4 years. Average interval between initial diagnosis and nephrostomy: 13.3 months. Average survival following nephrostomy: 18.0 months. Average interval between initial diagnosis and death: 31.3 months. Two patients died during the post-operative period without ever being discharged. Eight patients survived longer than 12 months. There was no relationship between the degree of uraemia pre-operatively or the duration of the disease pre-operatively with the length of survival after nephrostomy.

4. Miscellaneous (Fig. 4). This group includes patients with carcinoma of the colon (7), ovary (4), pancreas (1) and vulva (1), along with 5 patients who had lymphoma and one with neuroblastoma. Average age at nephrostomy was 50.1 years. Average interval between initial diagnosis and nephrostomy: 22.7 months. Average survival following nephrostomy: 9.6 months. One patient with ovarian cancer, 2 with colon cancer, one with lymphoma, and one with carcinoma of the vulva lived longer than 10 months. The other 14 patients in this group died less than five months after nephrostomy.

Quality of Survival

An attempt has been made to estimate the quality

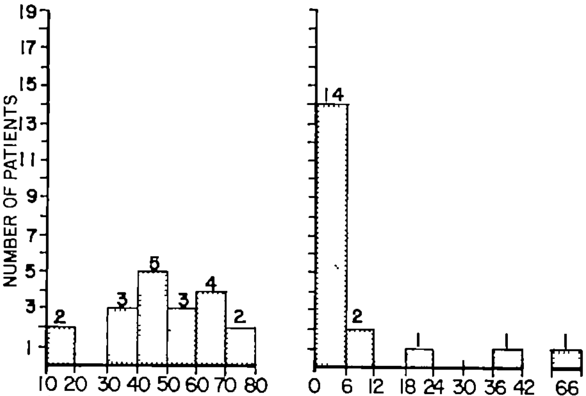

Fig. 4 Miscellaneous.

Table 5 Quality of Survival Following Nephrostomy Related to Type of Neoplasm

Neoplasm	*Quality of survival*					
	A		*B*		*C*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Cervix	3	20	10	67	2	13
Prostate	11	30	16	43	10	27
Bladder	3	10	11	38	15	52
Misc.	6	32	3	16	10	53
Total	23	23	40	40	37	37

of life for these patients after nephrostomy was performed. The following categories were used:

Group A: Patient was discharged home from the hospital. There was little or no pain and survival was at least 2 months. Patient was generally ambulatory, alert, and able to participate in family life or work.

Group B: Patient was discharged home or to a minimal care institution. Pain was controlled with analgesics and there was at least moderate limitation of activities.

Group C: Patient was confined to hospital with pain requiring narcotics, or a continuing decline in status.

The results relating these criteria to the various tumour types are listed in Table 5.

No major factors could be found which might be used as pre-operative indicators of whether nephrostomy might be expected to provide a reasonably long post-operative survival or good quality survival. The A group of patients averaged 56 years old, while the B and C groups averaged 64 years. Four of the 23 patients (17%) in group A carried significant diagnoses other than their carcinoma, while 23 of 77 (30%) of groups B and C had other significant disease documented. Unilateral or bilateral ureteric obstruction did not seem to be an important factor in quality of survival, nor did the type or extent of treatment before nephrostomy. The average duration of carcinoma prior to nephrostomy in group A was 34 months, while it was 25 months in groups B and C. The only factor which seemed to have any strong significance for the quality of survival seemed to be the site of the initial tumour and, in this respect, prostatic and cervical carcinoma seemed to hold more hope for somewhat better quality.

A dramatic reponse to nephrostomy in terms of blood urea and creatinine levels was seen in 19 of 23 group A patients, and in 60 of 77 patients from groups B and C. Only 2 post-operative complications occurred in group A patients, while 29 occurred in others. Most significantly, 19 of the group A patients underwent further treatment directed at their carcinoma, while only 40 of the other 77 had treatment subsequent to nephrostomy. This was due to the terminal status of many of these patients.

Discussion

Obstructive uropathy is a relatively common problem in locally invasive and metastatic genitourinary malignancies, while it is quite rare as a complication of other malignancies (Presman and Ehrlich, 1948). It may occur in as many as 7% of patients with malignant lymphoma (Abeloff and Lenhard, 1974). Without relief of obstruction, a rapid deterioration to coma and early death will inevitably ensue. The urologist's dilemma is: what will happen if he does relieve the obstruction? The use of an indwelling silastic splint as advocated by Gibbons (Gibbons *et al.*, 1974) or of percutaneous nephrostomy raises this question to an even greater degree than open surgical nephrostomy. As these methods are less invasive and can be performed under local anaesthesia, the temptation to go ahead and relieve the obstruction before completely assessing the situation in the individual patient may be strong.

Eighteen per cent of our patients died without being discharged from the hospital after nephrostomy. In other series, this figure has been even higher: 38% (Brin *et al.*, 1975) and 43% (Grabstald and McPhee, 1973). This mortality rate and the preceding pain and misery for the patients should be carefully considered prior to performing a diversion. The high cost of prolonged hospitalisation is also a significant factor.

In any series such as this, it would seem that several selecting factors have already been involved: (*a*) the type and/or the stage of carcinoma may not be known pre-operatively (16% in our series); (*b*) a belief that further therapy is available and may improve the quality of life; (*c*) the presence of a septic state; (*d*) obviously terminal patients would not have nephrostomy recommended.

In spite of these selection guidelines, which may perhaps be followed unconsciously, the results in terms of length and quality of survival continue to be poor.

What factors can be seen to be of importance in deciding whether to divert or not?

(1) The patient's desire. This may not be the most important medical point, but it must be considered above all factors. Some patients may refuse nephrostomy, although they seem to be good candidates. Rapport and patient education are the physician's instruments of persuasion in such a circumstance. Occasionally, a patient may desire to prolong life even for a brief period, for legal or financial reasons. Such a wish should be respected.

Fearing death, many patients may request that everything possible be done to give them even a brief respite. They must be fully informed of the consequences of surgery, the possible complications, and the suffering that may lie ahead. Family consultation is at its most important in these cases. Open and frank discussion is mandatory.

(2) Pressure from other physicians. The radiotherapist or chemotherapist may feel that they can contribute to prolonging life. The urologist has the leading role in any surgical decision, but must consult with these colleagues and decide if they have anything to offer.

(3) Previously undiagnosed disease. There seems little doubt that nephrostomy should be strongly considered where the malignancy has been previously undiagnosed and, therefore, untreated.

(4) Effective therapy still available. Many diseases which have advanced to the point of causing ureteric obstruction will be refractory to any therapeutic modalities. With advances in chemotherapy, this may less frequently be true in the future. An obvious example of remaining therapy is bilateral orchiectomy. In our series, 19 of the patients with carcinoma of the prostate had bilateral orchiectomy prior to nephrostomy. Only 7 (37%) of these survived longer than one year. Of 9 patients who had bilateral orchiectomy after nephrostomy, 2 died in the early post-operative period from sepsis and gastrointestinal haemorrhage, but the remaining 7 survived more than one year. Michigan and Catalona (1977) have found an 88% response rate to bilateral orchiectomy in patients with ureteric obstruction secondary to carcinoma of the prostate, with poorer results from oestrogen therapy, antiandrogen or radiation.

(5) Site of primary malignancy. It is obvious that our patients with prostatic or cervical primaries did better than those in other groups. The same has been found in other series (Grabstald and McPhee, 1973; Brin *et al.*, 1975; Khan and Utz, 1975; Van Dyke and Van Nagell, 1975). One should be exceedingly careful in advising nephrostomy in the patient with transitional cell carcinoma of the bladder or colonic carcinoma, where survival rates and quality of life are dismal. Quality of life in our patients with prostatic or cervical carcinoma was generally good.

(6) Stage of disease. Obviously, the more localised the disease, the better. A survey for metastases should be performed, if possible, prior to nephrostomy. Unilateral ureteric obstruction has been a better situation than bilateral (Van Dyke and Van Nagell, 1975), although this was not true in our series.

(7) Other disease. In our series, the presence of associated illnesses was detrimental to the prognosis. Grabstald and McPhee (1973) found that associated anaemia was a very poor prognostic factor.

(8) Previous duration of disease. In prostatic carcinoma and to some extent in cervical carcinoma, a long prior history may indicate slowly advancing disease and encourage the belief that it may yet be a long time before the malignancy runs its course.

(9) Age of patient. This did not seem to be a major factor in our series, but we feel a greater urge to operate in the younger patient. This is a case, perhaps, where the physician's emotions must not be allowed to dominate critical judgement.

(10) Emotional stability of the patient. Will he be able to endure the problems which are likely to arise in the future? Will he return to any useful activities? Will he place an overwhelming burden on his family?

Other Considerations

Peritoneal dialysis was used pre-operatively in only one of our patients. In most instances, anaesthesia would be well tolerated and urinary drainage is a better form of treatment than dialysis. Haemodialysis may be indicated where uraemia is secondary to renal infiltration by malignancy (Baumgartner *et al.*, 1976), but not in obstructive cases.

Ureteric catheterisation is difficult in patients with obstruction due to malignancy and, in many patients, the use of Gibbons' catheters may be impossible. Percutaneous nephrostomy is an excellent temporary measure, but does not provide reliable drainage of a kidney for long periods. Nephrostomy will, therefore, continue to be performed in many of these patients. We feel that the use of a silastic loop nephrostomy is superior to a Foley catheter, as the multiple drainage holes are less likely to become obstructed, the catheter is less likely to be pulled out, it is less reactive, and it needs less frequent changes (Hawtrey *et al.*, 1974).

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Investigations Using Autoradiographic Analysis of Urinary Stones

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Summary—Sections of a urinary stone were examined using autoradiographic analysis. The results obtained were compared with chemical analysis, undertaken on the same stone, to illustrate the effectiveness of the activation technique.

The importance of stone analysis has been stressed by a number of experimentalists in the field (Hodgkinson, 1971; Spector *et al.*, 1978).

The purpose of autoradiographic analysis is to examine the elemental distributions within the stone since some calculi have distinct variations in composition across the various strata. It is also important to obtain a pictorial distribution across whole sections of stone compared to ground-up samples which are used in "ordinary" chemical analyses.

Materials and Methods

Cross-sections of stones were mounted and irradiated in the cyclotron using charged particles. The technique was made quantitative by using standards. These standards contained known amounts of the elements of interest (*i.e.* carbon, oxygen, sodium, phosphorus and calcium), and were irradiated at the same time as the stone sections. Autoradiographs of standards and stone sections were obtained under identical conditions (on the same film) and percentage elemental compositions obtained from microdensitometer scans taken across the autoradiograph.

Results

A "staghorn-shaped" calculus was examined to illustrate the effectiveness of the technique. Carbon, sodium, oxygen and calcium were determined autoradiographically. The distribution of carbon (Fig. 1) is clearly defined in specific areas of intensity at approximately 11% carbon in the lighter area in the autoradiography to 2% carbon in the other regions.

The oxygen autoradiograph was exactly parallel to that of carbon, varying between 55±1% oxygen in the less dense regions.

The calcium distribution (Fig. 2), however, was the direct reciprocal to those of carbon and oxygen, showing variations of 21 to 26% calcium in the denser regions.

A chemical analysis was undertaken using a ground-up portion of material taken across the stone and 10.25% calcium and 27.29% oxalate were found.

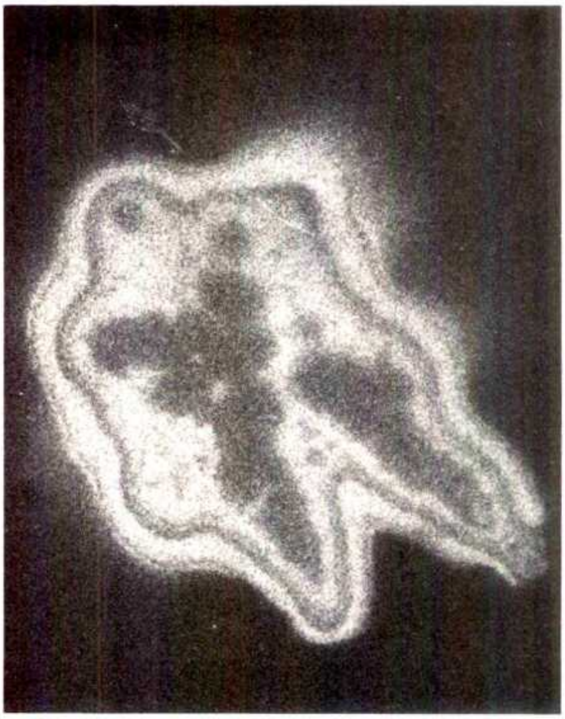

Fig. 1 Carbon autoradiography of staghorn calculus (×4).

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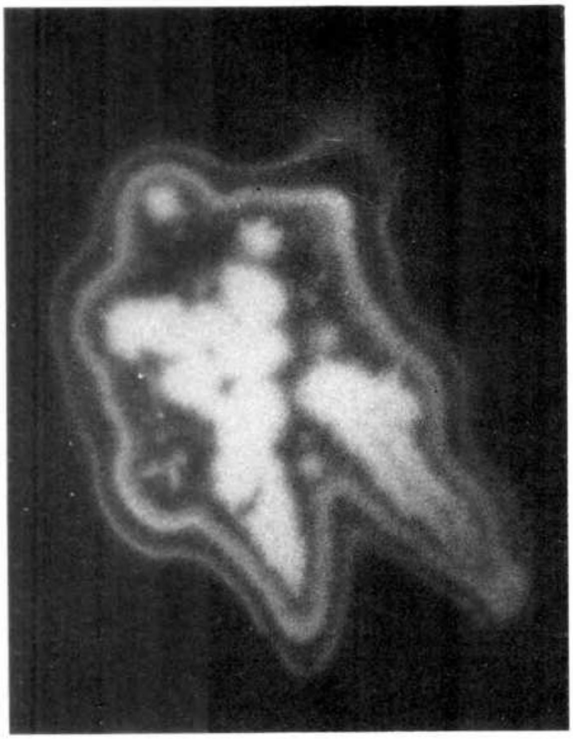

Fig. 2 Calcium autoradiography of staghorn calculus (×4).

Discussion

The autoradiographic analysis provides visual interpretation of the results since areas of intense elemental concentrations are clearly seen. Calcium was shown to be present in approximately 50% of the area across the stone and was seen to be present in discrete bands. Since these bands were found to contain between 21 and 26% calcium, the results correlate well with those obtained by the "averaged-out" percentage contribution obtained by chemical analysis.

Since ordinary chemical analysis uses ground-up portions taken from specific regions across or within the stone, it is possible that stones of mixed composition can provide erroneous results, since representative samples are not necessarily obtained.

In this respect autoradiographic analysis can augment existing techniques and provide for true representation of the results.

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A Study of Childhood Renal Tumours using Xenogeneic Antiserum

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Summary—Fifty-six primary childhood renal tumours, 14 normal and 12 fetal kidneys were examined for their staining reaction with xenogeneic anti-Wilms' antiserum. The antiserum was raised by injecting Wilms' tumour extracts into 6-month-old rabbits which had been rendered tolerant *in utero* with pooled normal kidney extracts.

Renal carcinomas, mesoblastic nephroma and a large proportion of tubular Wilms' tumours were stained by the antiserum. In contrast, 6 of 7 bone-metastasising renal tumours of childhood (BMRTC) failed to fluoresce when treated with the antiserum, suggesting that the BMRTC has a different origin from the other childhood renal tumours studied.

Several excellent descriptions recognising the embryonic nature of nephroblastoma (Wilms' tumour) were published during the latter part of the nineteenth century (Eberth, 1872; Cohnheim, 1875; Wilms, 1899). It is generally thought that the tumour arises from embryonic cells which are capable of differentiating into renal elements, connective tissue and muscle. Although the histological picture seen in Wilms' tumour varies greatly, only rarely is there difficulty in diagnosis (Marsden and Steward, 1976; Wigger, 1976). In general, the presence of abortive glomerulotubular condensates surrounded by a mesenchyme-like stroma is characteristic of this tumour. Numerous studies have been carried out in an attempt to relate the histological appearance to the prognosis in nephroblastoma (Hardwick and Stowens, 1961; Bodian and Rigby, 1964; Jereb and Sandstedt, 1973; Perez *et al.*, 1973; Lawler *et al.*, 1975, 1977; Wigger, 1976). The limitation of such studies is well recognised and has been substantiated by a recent description of a primary renal tumour of childhood which has characteristic histological and ultrastructural appearances. This neoplasm occurs predominantly in boys and, unlike typical Wilms' tumour, appears to have such a marked tendency to metastasise to bone that it has been designated a bone-metastasising renal tumour of childhood (Marsden *et al.*, 1978; Marsden and Lawler, 1978; Morgan and Kidd, 1978). This finding has recently been confirmed (Beckwith and Palmer, 1978).

During the past few years, a number of papers have been published which report the presence of Wilms' tumour-associated antigens (Burtin and Gendron, 1973; Wise *et al.*, 1975; Burtin, 1976; Okada *et al.*, personal communication). We have raised an anti-Wilms' antiserum in 6-month-old rabbits which had been rendered tolerant *in utero* with pooled normal kidney extracts (Waghe and Kumar, 1977). It was decided to use this antiserum in an immunofluorescence study of normal kidney, fetal kidney, nephroblastoma, mesoblastic nephroma, and bone-metastasising renal tumour of childhood and adults, to see if immunological as well as morphological criteria would distinguish this bone-metastasising renal tumour of childhood.

Materials and Methods

Preparation of Antiserum

The preparation of an anti-Wilms' antiserum and its characterisation were recently published as a preliminary communication (Waghe and Kumar, 1977).

The normal gestation period in rabbits is approximately 4 weeks. In order to render rabbit fetuses tolerant, 3 female rabbits, 2 weeks after mating, were anaesthetised using oxygen, nitrous oxide and halothane gas mixture and laparotomy

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was performed taking aseptic precautions. All fetuses were injected with 0.2 ml of pooled normal kidney extracts *in utero*. The kidney extract was prepared by homogenising tissue fragments (3-4 mm^3 obtained from 3 normal kidneys as a 10% W/V suspension in 0.1 M phosphate buffered saline (pH 7.2)) for 2 min at 4°C. Only one of the 3 rabbits produced a full-term normal litter of 7 rabbits. Four of these litter mates were inoculated intradermally when 6 months old with 0.5 ml of pooled EDTA extract of 6 Wilms' tumours. EDTA extracts were prepared following the method of Allerton *et al.* (1971). Six more injections of Wilms' extracts were given at fortnightly intervals, and a week after the last injection the rabbits were bled and the sera separated, pooled and stored at —20°C in small aliquots.

Table Immunofluorescent Staining of Normal, Fetal and Malignant Renal Tissues Using Anti-Wilms' Antiserum

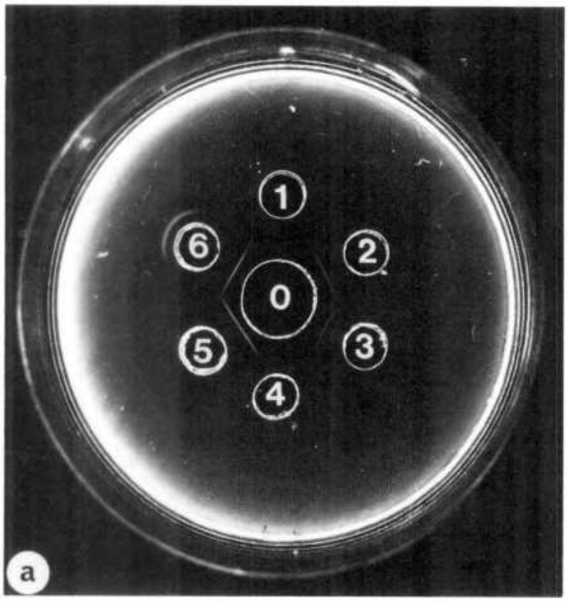
Source of tissues	*No. stained/ no. examined*	*Percentage*
1. Renal tumours		
A. Wilms' tumour		
(*a*) tubular	33/35	94
(*b*) non-tubular	4/9	44
B. Mesoblastic nephroma	1/1	100
C. Bone-metastasising renal tumour of childhood	1/7	14
D. Renal carcinoma	3/4	75
2. Normal kidneys	0/14	0
3. Fetal kidneys	2/12*	17

* Ages of kidney in weeks and numbers examined shown in parentheses: 16 (2), 14 (4), 12 (2), 11 (2), 10 (1) and 9 (1).

The pooled antiserum was successively absorbed with freeze-dried tissue homogenates (100-200 mg/ml) of pooled fetal kidneys (12, 25, 31 and 37 weeks), pooled neonatal, and pooled normal adult kidneys, liver, thymus, neuroblastoma, mammary carcinoma and pooled human serum. Absorption with each of these tissue extracts was carried out for 24 h at 4°C and after each absorption the precipitate was removed by centrifuging at 20,000 g for 1 h. The antiserum will be referred to as absorbed antiserum (AS).

Immunodiffusion and Immunoelectrophoresis

Immunodiffusion and immunoelectrophoretic studies were carried out using 1% agar and 1% agarose respectively according to procedures described earlier (Waghe and Kumar, 1977).



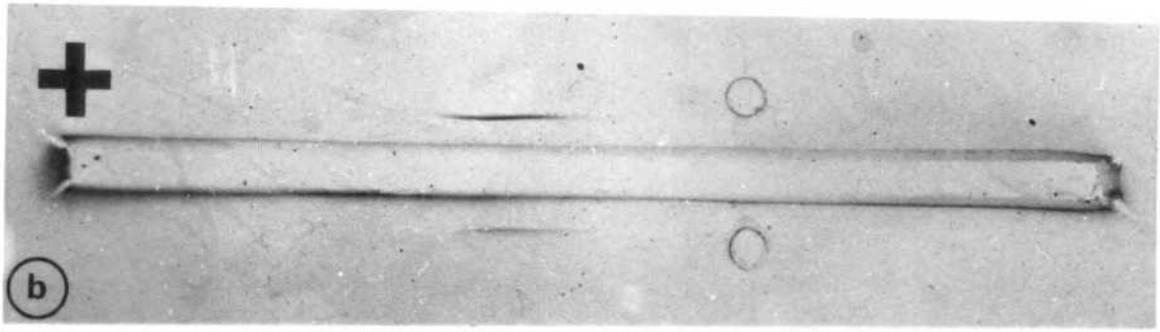


Fig. 1 (a) Gel diffusion studies using absorbed Wilms' antiserum (well 0). A complete reaction of identity can be seen between EDTA-extract of Wilms' tumour (wells 3 and 6), renal carcinoma (well 5) and mesoblastic nephroma (well 2). No precipitation line was produced by either normal (well 1) or fetal kidney (well 4) extracts. (b) Immunoelectrophoretic pattern of EDTA-extract of Wilms' tumour (top and bottom wells) developed with absorbed anti-Wilms' antiserum (central trough). Note a single precipitation anodic arc with α-mobility.

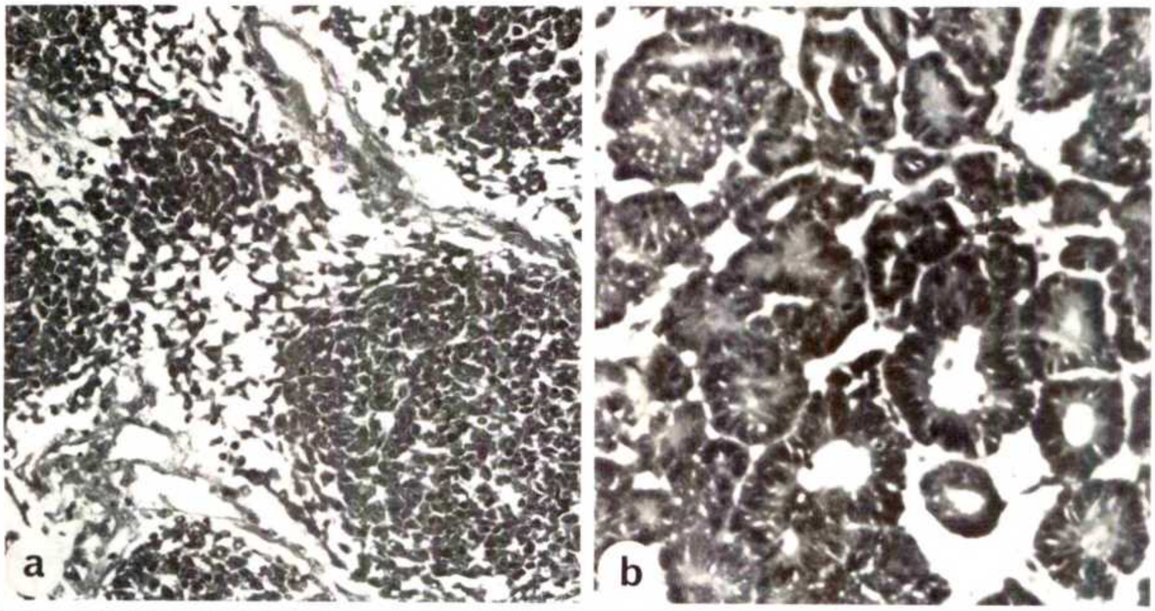


Fig. 2 (a) Undifferentiated Wilms' tumour showing islands of blastemal cells (H and E ×100). (b) Highly differentiated Wilms' tumour with tubules lined by columnar cells (H and E ×100).

Immunofluorescence (IF) Method

The majority of tissues used for sectioning were either fresh or stored as fragments in freezing medium containing 10% dimethyl sulphoxide in liquid nitrogen. Occasionally, sections of paraffin-embedded tissues were also used (see below). The details of various target tissues are:

(i) 44 Wilms' tumours.
(ii) 4 renal carcinomas.
(iii) 1 mesoblastic nephroma.
(iv) 7 bone-metastasising renal tumours of childhood.
(v) 14 normal kidneys: one was obtained from a full-term baby who died shortly after birth; 2 were surgical specimens removed for anatomical complications; 11 were autopsy specimens.
(vi) 12 fetal kidneys: these were collected from therapeutic abortions. The estimated gestation periods are given in the Table.

Fresh tissue sections (5 μ) were fixed in cold acetone for 10 min, air dried, and incubated with antiserum (AS) diluted 1:20 in PBS for 20 min at room temperature. The controls were treated with an equivalent dilution of normal rabbit serum. After thorough washing for 30 min, the sections were incubated with fluorescein isothiocyanate-labelled goat anti-rabbit serum (1:40 dilution Wellcome Laboratories, Beckenham, Kent, England) for 20 min at room temperature, washed for 40 min and mounted in glycerol-saline (1:1) and examined under an incident light fluorescence microscope. In order to avoid bias all slides were read blind.

Paraffin sections for IF studies were prepared

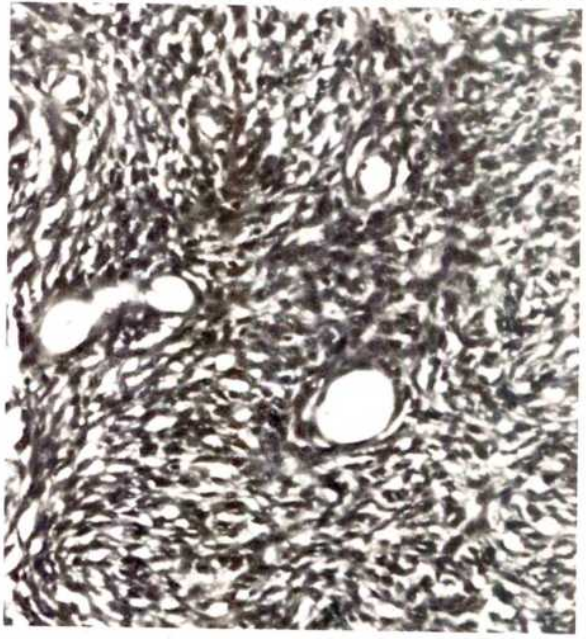


Fig. 3 Bone-metastasising renal tumour showing polygonal cells with delicate nuclear chromatin and prominent capillaries (H and E ×100).

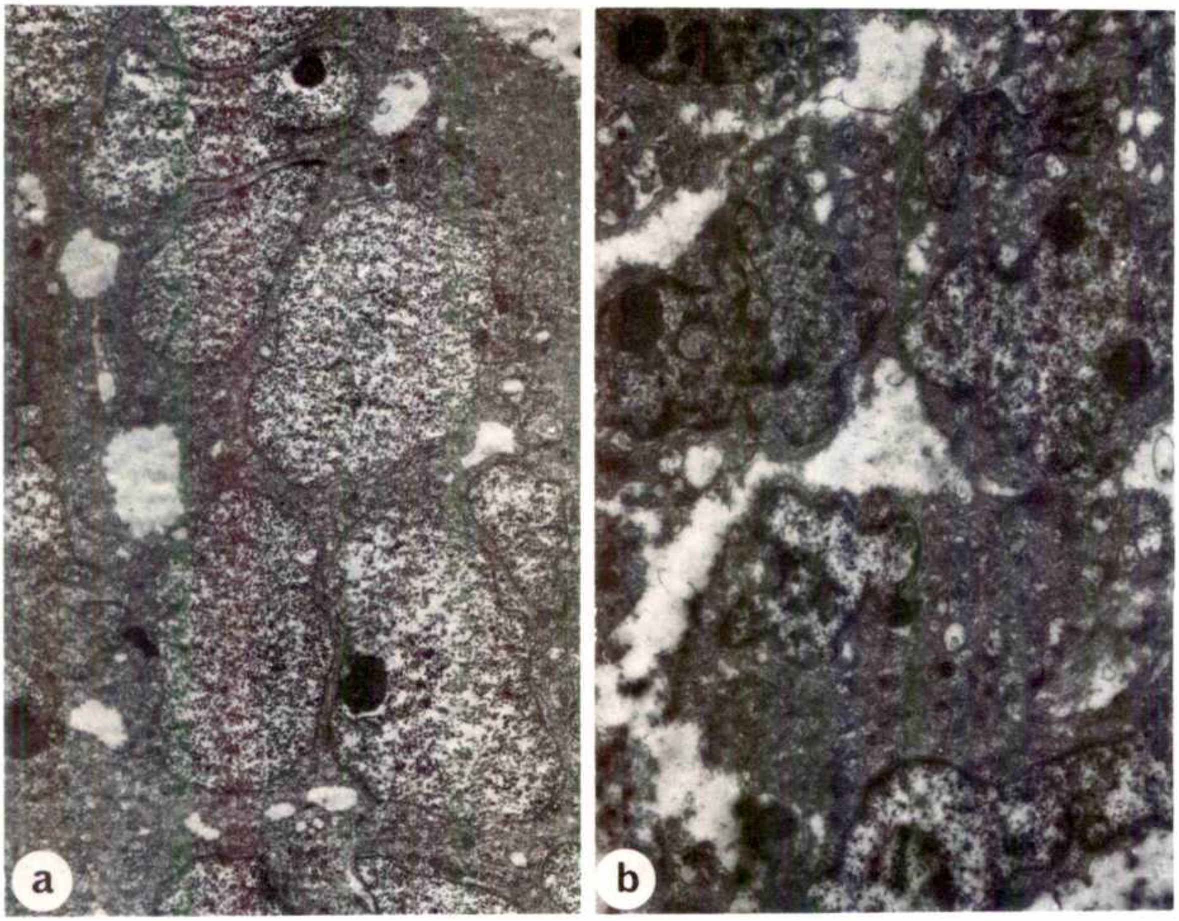


Fig. 4 (a) Electron micrograph showing part of a typical cord of cells in the bone-metastasising renal tumours of childhood. The cells have both epithelial and mesenchymal features (uranyl acetate and lead citrate stain ×4000). (b) Same BMRTC cells with a more mesenchymal appearance. Intercellular spaces containing collagen occur frequently (uranyl acetate and lead citrate stain ×6200).

as recommended by Nairn (1969). After removal of paraffin and overnight washing in distilled water, these sections were treated as above.

Results

In accordance with an earlier finding, the absorbed antiserum produced a single precipitation line against 4 Wilms' tumour extracts and renal carcinomas in both gel diffusion and immunoelectrophoresis (Fig. 1). A precipitation line was not observed against either normal kidneys or those obtained from fetuses more than 12 weeks old. Recently, however, when it became possible to test 2 kidneys from 9- and 10-week-old fetuses, a complete reaction of identity was observed between Wilms' tumours and fetal kidney extracts. Absorption of the "absorbed antiserum" with pooled 9- to 10-week fetal kidney extracts completely abolished its ability to react with the respective fetal kidney and Wilms' tumour. Similarly, absorption of the antiserum with Wilms' tumour homogenates abrogated its ability to react with both fetal kidneys and Wilms' tumour extracts.

The findings of the immunofluorescence studies using antiserum (AS) are presented in the Table. None of the 14 normal kidneys stained with AS. The ages of the donors of these kidneys are shown in the same Table. In the previous study only 4 fetal kidneys, viz. 12, 25, 31 and 37 weeks old, were studied. In contrast to our previous findings (Waghe and Kumar, 1977), kidneys of 9- and 10-week-old fetuses showed a diffuse but strong intracytoplasmic immunofluorescence. The estimated ages of 12 different fetuses from which kidneys were obtained are shown in the Table, from which it can be seen that although kidneys from 2 11-week-old and 2 12-week-old fetuses were examined, none of the 4 stained by the antiserum. The non-staining of 12-week-old fetal kidney is understandable, since homogenate of 12-week-old kidney was used in absorption of pooled serum. Kidneys from fetuses earlier than 9 weeks were not examined.

A brief summary of histological features of renal tumours is included here so that our IF results can be related to histological components.

Nephroblastomas can be classified as either tubular or non-tubular (Fig. 2). The appearance of tubules varies considerably; different types of tubules in varying stages of differentiation can often be seen in the same tumour. The bone-metastasising renal tumour of childhood shows histological features which are present in varying proportions. The predominant component consists of polygonal cells and a prominent capillary pattern (Fig. 3). The features which characterise these tumours as different from nephroblastoma are the absence of blastema and epithelial structures and the fact that the only mesenchymal differentiation is fibroblastic. Electron microscopic examination shows that the tumour cells share some features with normal mesangial cells (Fig. 4). The mesoblastic nephroma is made up of fibroblastic spindle cells in which embedded renal tubules and glomeruli may be seen. The tumour cells are not hyperchromatic as in undifferentiated nephroblastoma (Fig. 5). Renal carcinoma consists of rather characteristic large, clear or granular cells (Fig. 6).

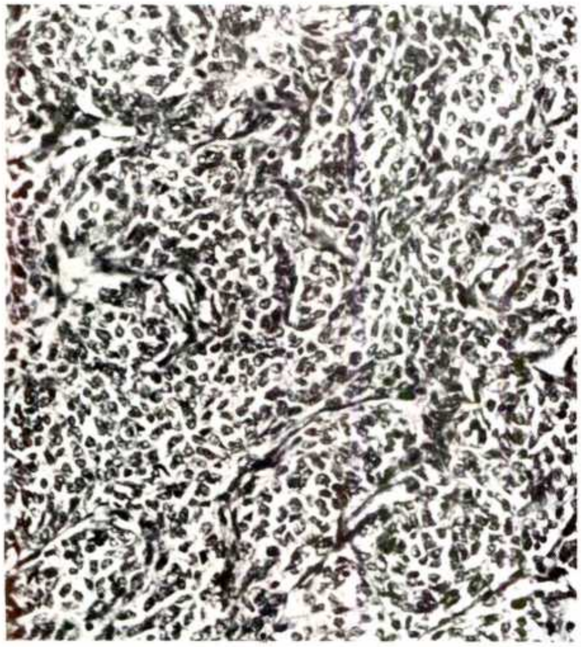


Fig. 5 Mesoblastic nephroma consisting of spindle-shaped fibroblastic cells with embedded cuboidal-lined tubules, some of which have flattened epithelium (H and E × 100).

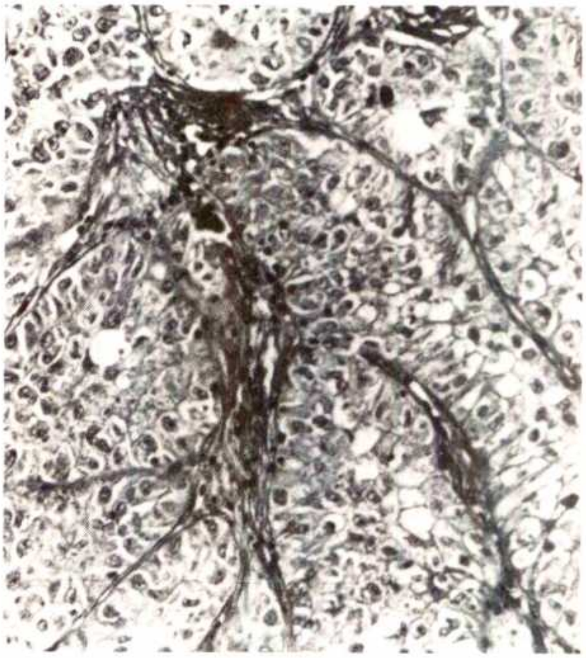


Fig. 6 Renal carcinoma with large cells showing alveolar grouping. Many of the cells are distended and possess clear cytoplasm (H and E × 100).

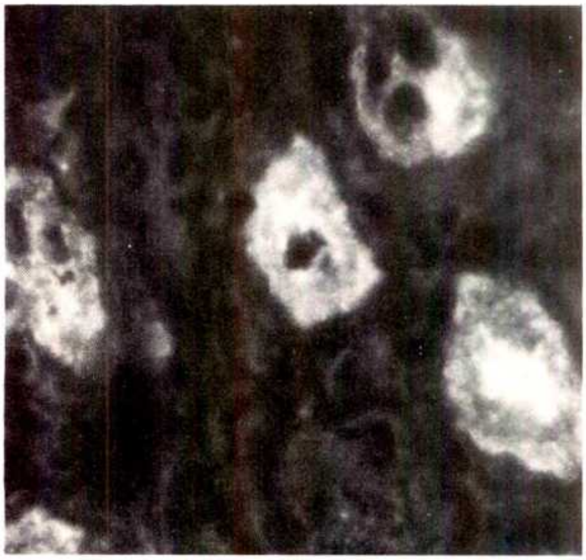


Fig. 7 Indirect immunofluorescence of staining of tubular Wilms' tumour with absorbed anti-Wilms' antiserum. The strong staining of tubules is apparent.

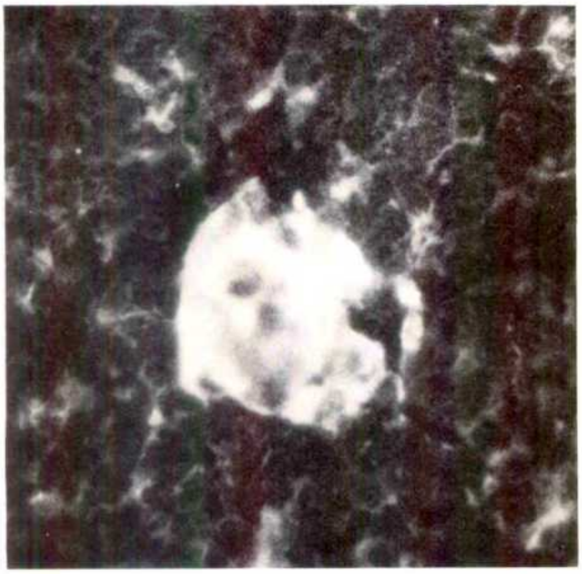


Fig. 8 Indirect immunofluorescence of "tubular" Wilms' tumour with absorbed anti-Wilms' antiserum. Note: strong fluorescence of an undifferentiated structure.

A large proportion (94%) of tubular Wilms' tumours were stained by the antiserum (Fig. 7). In this group of tumours the most frequent site of reaction was in the tubules; in some instances, more widespread staining of undifferentiated structures which did not form any obviously organised structures was also seen (Fig. 8). The fluorescent staining of non-tubular Wilms' tumours and renal carcinomas was diffuse and not limited to any one cell component in particular (Fig. 9). In mesoblastic nephroma, the tubules fluoresced more strongly than any other cellular part.

The staining pattern of the only positive bone-metastasising renal tumour of childhood was unusual. There were numerous apparently isolated focal areas wherein a positive collar, several cells in thickness, was seen around a negative central core. There was no reason for this particular pattern of staining, as examination of the equivalent H and E stained sections failed to reveal any difference between cells comprising the central core and the periphery.

Discussion

We have identified a new oncofetal antigen, to be called oncofetal Wilms' antigen (OWA), which is present in the majority of Wilms' tumours, especially the tubular variety, and in 9- and 10-week-old but not older fetal kidneys. A number of other studies exist wherein oncofetal antigens have been demonstrated in non-renal tumours by using xenogeneic antiserum. In such studies, cross-reacting antigens in fetal tissues have been found not to be restricted to a particular fetal age group. Our finding of cross-reacting antigens between early fetal kidney and Wilms' tumour is not unique. For instance, Brown *et al.* (1975) raised antisera against human acute lymphoblastic leukaemia cells (ALL) and found that their antisera reacted only with 9- to 13-week fetal liver and ALL cells but not against livers from fetuses that were more than 16 weeks old.

The present antigen (OWA) is different from any of the previously described Wilms' tumour-associated antigens or substances. Unlike Wise *et al.* (1975), we failed to detect cross-reactivity between OWA and fetuin present in fetal and new-born calf serum. The antigenic substance described by Wise *et al.* is a trypsin-sensitive polyanionic mucoprotein of α-mobility, whereas OWA is trypsin-insensitive and anionic. Our antigen shares some properties with W-antigen described by Burtin and Gendron (1973) in that both antigens are anionic, insensitive to trypsin and are present in both Wilms' tumours and renal carcinomas. However, W-antigen is absent in fetal kidneys, whereas OWA is detectable in early stage fetuses. Burtin (1976) has identified another

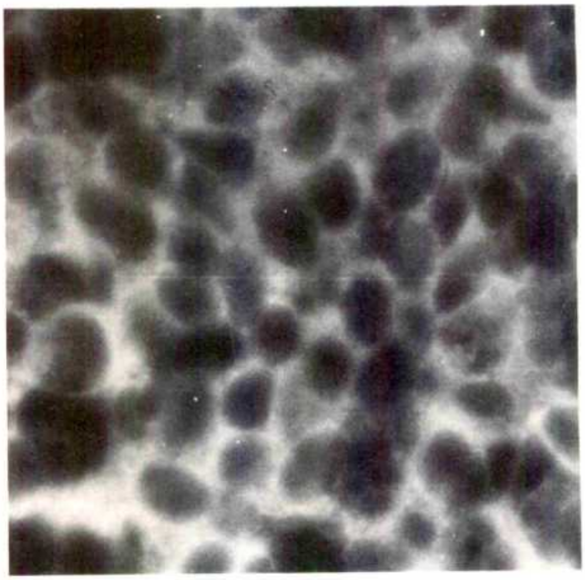


Fig. 9 Indirect immunofluorescent staining of renal carcinoma with absorbed anti-Wilms' antiserum. The pattern of fluorescence is diffuse and not limited to any one cell type or component.

nephroblastoma-associated antigen which does not cross-react with his W-antigen. This new antigen also differs from OWA as it is trypsin-sensitive and on electrophoresis it migrates to the γ and post γ area. OWA antigen also differs from the nephroblastoma-specific antigen of Okada (Okada, personal communication) which is cationic and trypsin-sensitive.

OWA differs from another antigenic substance called TAMM-HORSFALL (T-H) protein. Tamm and Horsfall in 1952 identified a protein in normal human urine which was later found to be a glycoprotein of 80,000 molecular weight (Fletcher *et al.*, 1970a, b). Wallace and Nairn (1971) prepared antisera against T-H protein, and using an immunofluorescence technique located it in distal convoluted tubules, loops of Henle and embryonic kidneys from 8-week to full-term pregnancy. In the following year, the same authors found that 10 of 11 renal carcinomas did not contain T-H protein. On the other hand, both of the Wilms' tumours examined were positive for this protein. Thus, unlike the T-H protein, OWA is present in both renal carcinoma and nephroblastoma but is not detectable in fetal kidneys older than 10 weeks.

Histologically, nephroblastoma is a complex tumour and consists of a variety of cell types and structures which often vary in their degree of differentiation and organisation in different parts of the same tumour. It is therefore not surprising that attempts at histopathological classification have not won unanimous acceptance (Marsden and Steward, 1976; Wigger, 1976). This problem has been compounded by the recent recognition of a new histological type of primary renal tumour which has a markedly worse prognosis than Wilms' tumour. This tumour has been designated "bone-metastasising renal tumour of childhood" (Marsden *et al.*, 1978; Marsden and Lawler, 1978) or "clear cell sarcoma" (Beckwith and Palmer, 1978). From our results, it is apparent that the majority of Wilms' tumours, mesoblastic nephroma, renal carcinomas and early fetal kidneys share a common antigen which is absent from nearly all of the BMRTC examined. The presence of cross-reacting antigen between Wilms' tumour and renal carcinomas supports our earlier lymphocytotoxicity results wherein lymphocytes from patients with renal carcinomas proved highly cytotoxic to tissue-cultured Wilms' tumour target cells (Kumar *et al.*, 1972).

The more frequent staining of tubular Wilms' tumours compared with non-tubular is difficult to understand. Rousseau-Merck *et al.* (1977) found that *in vitro* co-cultivation of chick and mouse embryonic tissues with Wilms' tumours resulted in an increase in the number of tubules in the latter. It will be interesting to determine whether the "inducers" can alter the IF of non-staining Wilms' tumours which either lack or possess undetectable amounts of OWA antigen.

Failure of our antiserum to stain BMRTC raises a possibility that this neoplasm originates differently from Wilms' tumours. Wallace and Nairn (1972) used 2 antisera, one reacting with Brush Border (BB) protein of proximal convoluted tubules and the other with a Tamm-Horsfall (T-H) protein reacting with distal tubules. Their IF study showed that renal adenomas and renal carcinomas arise from proximal convoluted tubules, since they contain BB antigen found nowhere else in normal kidney. In contrast, Wilms' tumour contained both BB and T-H antigens, indicating that these neoplasms contain primitive metanephric tissue which is capable of differentiating in several directions. Although the histogenesis of BMRTC is unknown, a possible origin from mesangial or interstitial cells has been suggested (Marsden *et al.*, 1978). In order to obtain definite evidence of the histogenesis of the various histological types of renal tumours, it will be necessary to raise antisera of different specificities. Meanwhile, we intend to continue to use the present anti-Wilms' antiserum to study more primary renal tumours in children.

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The Diagnosis and Management of Benign Fibrous Ureteric Polyps

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Summary—The diagnosis and management of benign fibrous ureteric polyps are discussed.

A pre-operative diagnosis is suggested by a long history of loin pain or haematuria, or both, in a younger patient with the radiological findings of ureteric obstruction or a radiolucent ureteric filling defect.

The diagnosis is confirmed at operation by opening the ureter and exposing characteristic fronds of polyps arising from a common base.

It is suggested that management should be conservative local excision and not nephroureterectomy, as previously practised.

Benign ureteric polyps have previously been recorded. In a review of the world literature, Abeshouse (1956) described 592 primary ureteric tumours and of these 139 were benign. Earlier reports did not, however, differentiate between benign fibrous ureteric polyps and Grade 1 transitional cell carcinoma. The first report of a benign neoplasm of the ureter was by Lebert in 1861; histologically it was a polypoid fibroma.

Patients

This paper presents the clinical details of 12 cases in the St Peter's Group of Hospitals and in St Bartholomew's Hospital, London. The English literature has also been reviewed and a further 30 cases identified, making a total series of 42 cases.

In reviewing the literature, many other probable cases were rejected as they were not clearly differentiated from transitional cell carcinoma.

Clinical Characteristics

The typical presentation is that of a young patient with a long history of intermittent loin pain and haematuria (Table 1). The preponderance for the left side and the male sex is unexplained. Abeshouse (1956), in a previous series, also found that benign tumours of the ureter were more common on the left, whereas malignant ones were more evenly distributed.

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Pathology

Macroscopically, the polyps were either single or multiple smooth fronds arising from a common base (Fig. 1). Sometimes they arose from several areas in the ureter. The usual site was in the region of the pelviureteric junction but they also occurred in other sites in the ureter and were seen extruding from the ureteric orifice. Ulceration of the tip was also seen.

Microscopically they consisted of a cone of fibrovascular stroma covered with a single layer of normal transitional cell epithelium with no evidence of papillary formation (Fig. 2).

Diagnosis

The radiological findings are summarised in Table 2 and are mainly non-specific. The classical description is of a corkscrew filling defect in the

Table 1 Clinical Characteristics of Benign Ureteric Polyps (42 Cases)

Site	50% pelviureteric junction
Sex	71% male
Age (mean)	39 years (range—birth to 65 years)
Length of history (mean)	5.5 years (range—hours to 30 years)
Pain (total)	79%
Haematuria (total)	57%
Haematuria and pain combined	38%
Other presentation	5%
Bilateral involvement	7%

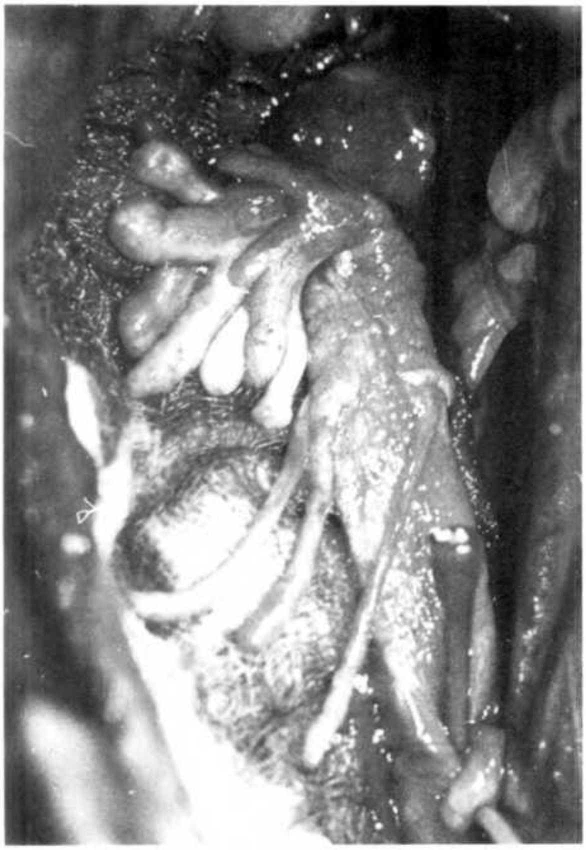

Fig. 1 Ureter opened at operation to show polyps.

upper ureter, as shown in Figure 3, but this is not often seen.

Other abnormalities were hydronephrosis, ureteric obstruction or ureteric filling defect. Other findings were a non-functioning kidney in 3 cases, whilst no abnormality was detected in 5 intravenous urograms and 2 retrograde ureterograms.

In all cases in which it was performed, cytology was normal.

In the majority of cases the diagnosis was made at operation and in some cases was made by a pathologist. Only rarely was the diagnosis considered pre-operatively.

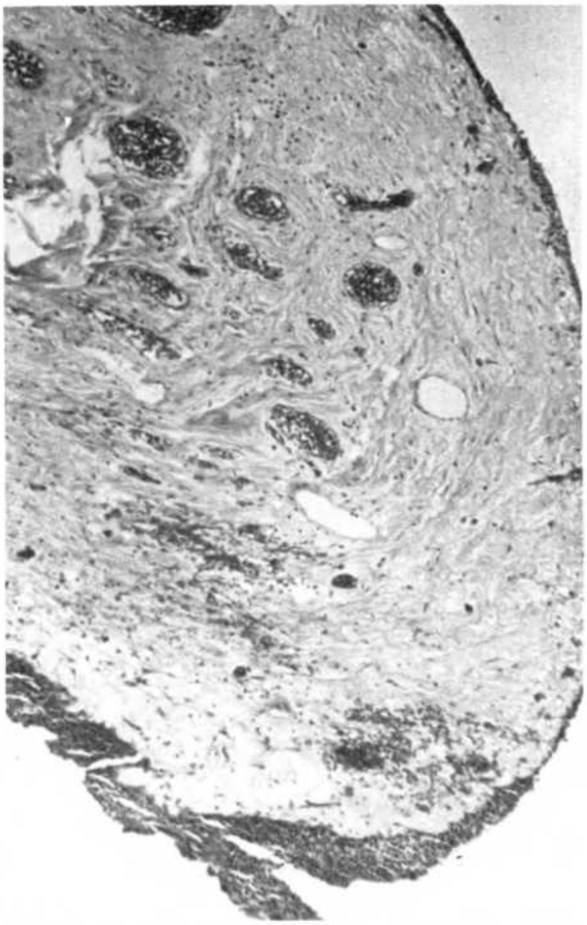

Fig. 2 Photomicrograph of tip of a benign fibrous ureteric polyp (H and E × 85).

Management

Most cases (Table 3) have in the past been treated by radical surgery, such as nephroureterectomy. All of our 12 cases and some others in the literature have received conservative surgery, such as local excision of the polyps or of the pelviureteric junction, which has given excellent results.

It would appear that in most cases radical surgery was carried out when the diagnosis was in

Table 2 Radiological Findings (42 Cases)

	Performed	*Hydronephrosis/ obstruction*	*Filling defect*	*Other*	*N.A.D.*
Intravenous urogram	90%	59%	26%	8%	11%
Retrograde ureterogram	79%	45%	48%	—	6%
Both investigations showing same results (% of total cases)	—	42%	15%	—	0%

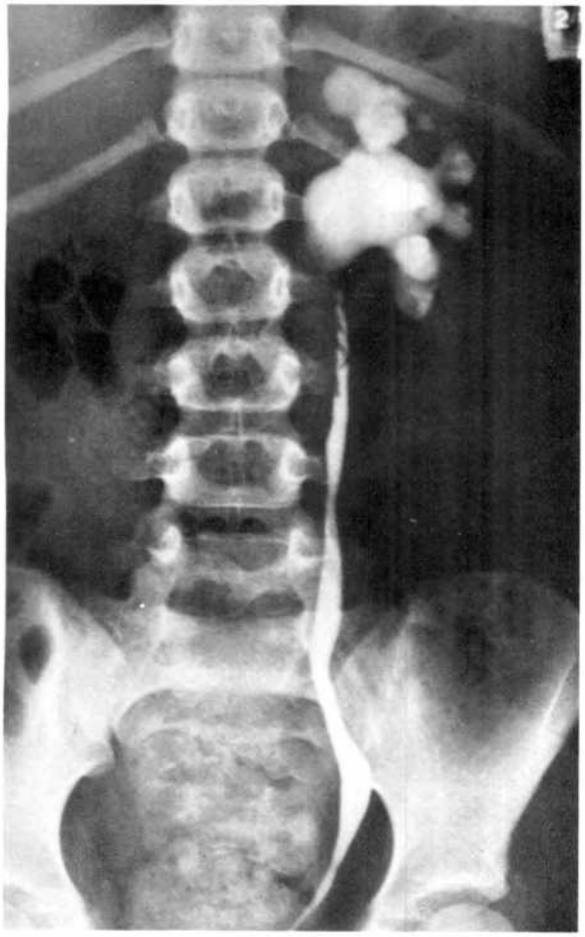

Fig. 3 Retrograde ureterogram showing corkscrew filling defect in upper ureter and hydronephrosis.

doubt and the tumour was thought to be malignant.

Discussion

Fibrous ureteric polyps are benign tumours of mesodermal origin and can be differentiated from epithelial tumours by the normal transitional cell epithelium covering the surface. In the earlier literature this distinction was not always recognised, and tumours of transitional epithelium were described as benign polyps.

As fibrous ureteric polyps are always benign tumours, it is thought that the management should be conservative. Unfortunately, in the majority of cases reviewed, the diagnosis was not made pre-operatively, the tumour was thought to be malignant and radical surgery was undertaken.

The diagnosis should be considered in a patient below the age of 40 who gives a long history of loin pain with or without haematuria, and whose intravenous urogram shows either a filling defect or ureteric obstruction. In these cases, cytology will help to exclude a transitional cell carcinoma. In doubtful cases the ureter should be opened at the time of surgery and the diagnosis made on the characteristic appearances. If urinary cytology is negative, it is unlikely that a malignant lesion is present, so that the risk of implantation should be minimal. Frozen section is of doubtful value, since it is difficult to interpret and in one case (Eilenberg *et al.*, 1977), resulted in unnecessary nephroureterectomy.

We feel that the operation of choice is resection of the tumour-bearing segment of the ureter or, if this is not technically possible because the changes are widespread, a local excision of individual polyps.

The aetiology of this condition is unknown. Theories suggested include obstruction, trauma, hormonal imbalance, infection or a developmental defect. As cases are often seen in children and even at birth (Soderdahl and Schuster, 1969), a developmental basis is possible. It has been suggested (Soderdahl and Schuster, 1969) that they are formed by an abortive attempt at duplication of the ureter.

Most patients have a pelviureteric obstruction which may be a significant factor.

Table 3 Management of Cases Recorded

	Total (%)	*Follow-up*	
		Range	*Mean*
Local excision	27%	6 months to 16 years	5.3 years
Local excision and fulguration of base	5%	1 month to 7 years	4 years
Excision of pelviureteric junction or segment of ureter	18%	9 months to 8 years	2.5 years
Nephroureterectomy	49%	3 months to 16 years	2.5 years

It is important for the surgeon to be aware of the condition and its benign nature as it is frequently diagnosed only at operation, especially operation for pelviureteric obstruction.

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Ureteric Ectopy in Children

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Summary—Twenty-eight cases of ectopic ureters are reviewed. Two groups consisting of single ectopic ureters and ectopia associated with duplex systems are considered. The former is associated with a high incidence of congenital anomalies. A dilated ectopic ureter remains completely extravesical but can produce features closely resembling those of an ectopic ureterocele. The use of ^{99m}Tc-DMSA renal scan has proved helpful in the diagnosis of the condition because it can demonstrate the existence of a poorly functioning kidney not evident on excretion urography.

An ectopic ureter is one which opens anywhere other than on the posterolateral extremity of the trigone (Greene, 1967). Symptoms referable to it generally occur only if the ureter opens outside the urinary tract or into the urethra.

In the male, the ureteric orifice is always proximal to the external sphincter; it may be in the posterior urethra, the ejaculatory duct, the seminal vesicle or the vas deferens.

In the female, the ureter may open anywhere in the posterior aspect of the urethra, in the vestibule in proximity to the urethral meatus or the hymen, into the vagina (Johnston and Davenport, 1969; Prewitt and Lebowitz, 1976; Gibbons and Duckett, 1978), uterus (Weiss and Dykhuizen, 1967) or Gartner's duct (Van Houtte, 1970).

Rarely, in either sex, an ectopic ureter may open into the rectum (Uson and Schulman, 1972).

Patients

From 1958 to 1978, 28 children with ectopic ureters have been treated by one surgeon (J. H. Johnston) at Alder Hey Children's Hospital, Liverpool. Two groups were recognised. Group I consisted of 15 children with 18 single ectopic ureters. Group II comprised 13 children in whom the ectopic ureter was one of a duplex system. This fortuitous occurrence of equal numbers of children in the 2 groups was considered most opportune for comparison.

Apart from 3 children who were lost to follow-up, all have been observed until they were considered fit to be discharged to the care of their referring general practitioner.

Table 1

Single ectopic ureters		*Ectopia with duplex system*	
Group I		*Group II*	
15 Children	18 Ureters	13 Children	13 Ureters
9 Females	6 Males	12 Females	1 Male

Clinical Features

Tables 1 and 2 show the sex incidence and age of the children at presentation in the 2 groups. The female to male ratio was 3:2 in Group I and 12:1 in Group II.

Seven of the 15 children in Group I presented within the first few days of life because of other congenital anomalies. Four infants had a low type of imperforate anus and one had a high type. One child presented with a myelomeningocele and another with eventration of diaphragm requiring immediate surgery.

In Group II there was one infant who presented on the day of birth with oesophageal atresia. On routine pyelography he was found to have an absent kidney on one side and an ectopic ureter on the other. It is apparent that there was a much

Table 2 Age at Presentation

	Group I	*Group II*
0-1 month	7	1
1 month-2 years	1	2
3-11 years	7	11

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Table 3 Associated Congenital Anomalies

Group I		*Group II*
Imperforate anus	5	Oesophageal atresia and absent kidney in 1 child
Myelomeningocele	1	
Eventration of diaphram	1	
Absent radius		
Congenital heart disease		
Multicystic kidney		
Horseshoe kidney		

higher incidence of associated congenital anomalies in Group I than in Group II (Table 3).

The right and left sides were equally affected in both groups. In 3 cases in Group I the condition was bilateral. The ectopic ureteric orifice was situated in the urethra in 57% and in the vestibule (in proximity to the urethral meatus) in 14%. In 18% of cases the ectopic orifice could not be located (Table 4).

Symptoms

Among the 21 females, 12 presented between the ages of 3 and 11 years with symptoms of constant urinary dribbling; 7 of these voided with a normal urinary stream. In 4 of these cases the ectopic ureter opened on the vulva, in one in the vagina and in 4 in the lower urethra; the orifice was unlocated in 3 girls. Three other girls between the ages of 6 weeks and 2 years had recurrent urinary tract infection which prompted excretion urography. In 2 of these cases the ectopic ureteric orifice could not be identified and in one case it opened into the urethra.

Three girls with bilateral single ureteric ectopia presented in the neonatal period with imperforate anus and a rectovestibular fistula; 2 neonates had a myelomeningocele and oesophageal atresia. In all of them it was impossible to assess their urinary continence. Diagnosis was made on excretion urography. The infants with bilateral single ureteric ectopia had dilatation of their upper renal tracts and the bladder failed to visualise in 2 of the 3.

Table 4 Position of Ectopic Ureteric Orifice in 28 Children

	Group I	*Group II*	*Total*
Urethra	9	7	16 (57%)
Vestibule	1	3	4 (14%)
Seminal vesicle	2		2 (7%)
Vagina	1		1 (4%)
Unlocated	2	3	5 (18%)

Table 5 Urographic Findings in Group I (15 Children)

12 children with unilateral single ectopia			
Ipsilateral kidney		*Contralateral kidney*	
Non-function	10	Normal	7
Hydronephrosis	2	Duplex system	1
		Caliectasis	1
		Hydroureteronephrosis	2
Horseshoe kidney	1		
Bilateral single ectopia	3		

One child presented for investigation of recurrent abdominal pain and an excretion urogram revealed her urological anomaly. Her ectopic ureter opened into the proximal urethra.

Urinary symptoms were not a remarkable feature among the male children. Three boys presented at birth, 2 with imperforate anus and one with eventration of diaphragm; one infant presented with epididymitis, one with haematuria after abdominal trauma, one with a renal mass, and one boy had nocturnal enuresis with post-micturition dribbling.

Investigations

The urographic findings are listed in Tables 5 and 6. In Group I there were 12 children with unilateral single ectopia. Urography showed the ipsilateral kidney to be non-functioning in 10 cases and hydronephrotic in 2. In one case of hydronephrosis it formed the ipsilateral half of a horseshoe kidney. The contralateral kidney was normal in 7 children, showed caliectasis in one and hydroureteronephrosis in 2. In one child the latter resulted from vesicoureteric reflux, and in the other child with multiple congenital anomalies the cause was undetermined. In bilateral cases, 2 girls had bilateral hydroureteronephrosis and one had hydroureteronephrosis on one side and a multicystic contralateral kidney.

In Group II, the ipsilateral kidney in the 13 children showed a non-functioning upper moiety in 6 and hydronephrosis of the upper pole in 7. The contralateral kidney showed a non-pathological duplex system in 6, a normal single system in 6 and agenesis in one. Six of the ectopic ureters

Table 6 Urographic Findings in Group II (13 Children)

Ipsilateral kidney		*Contralateral kidney*	
Non-function of upper pole	6	Normal duplex system	6
Hydronephrosis of upper pole	7	Normal single system	6
		Renal agenesis	1

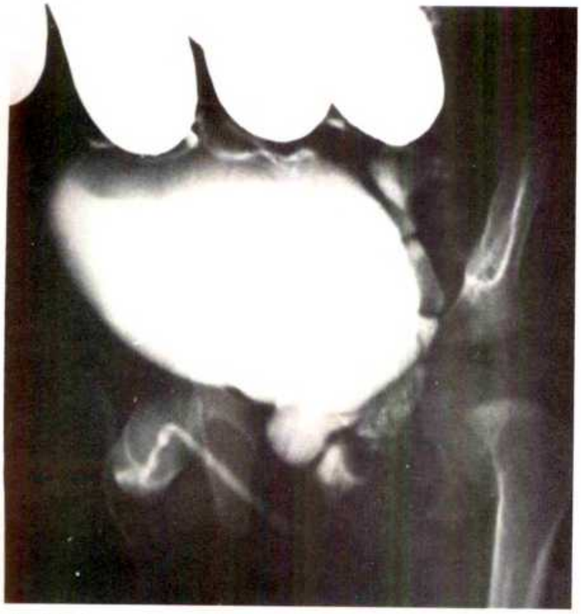


Fig. 1 Expression cystourethrogram of a boy, showing reflux of contrast medium from the posterior urethra into the seminal vesicle, vas deferens and thence into the ectopic ureter.

which opened into the urethra were demonstrable by urethroureteric reflux on voiding or expression cystourethrography. In 2 boys, reflux of contrast medium occurred from the posterior urethra into the seminal vesicles and vas deferens and thence into the ureter (Fig. 1).

Table 7 Treatment

Group I		*Group II*	
Nephroureterectomy	8	Heminephroureterectomy	10
Pyelopyelostomy	1	Ureteropyelostomy	1
Urinary diversion	4	Urinary diversion	1
Reimplantation of ectopic ureter	2	Reimplantation of ectopic ureter	1

Treatment (Table 7)

In Group I, nephroureterectomy of the ipsilateral kidney was performed in 8 children. Excision of the ectopic ureter and pyelopyelostomy, where the renal pelvis of the hydronephrotic half of a horseshoe kidney was anastomosed to the contralateral renal pelvis, was performed in one child. Four children required urinary diversion. Terminal ureterostomy was performed in 2 girls with bilateral single ectopia, because of gross hydroureteronephrosis and hypoplastic bladder (Fig. 2). One neonate required bilateral urinary diversion because of extremely poor renal function; he succumbed to his multiple congenital anomalies. One child required ureterosigmoidostomy because of an associated congenital vesicovaginal fistula. In 2 children an attempt was made to preserve the ipsilateral renal unit by implantation of the ectopic ureter into the bladder; no improvement

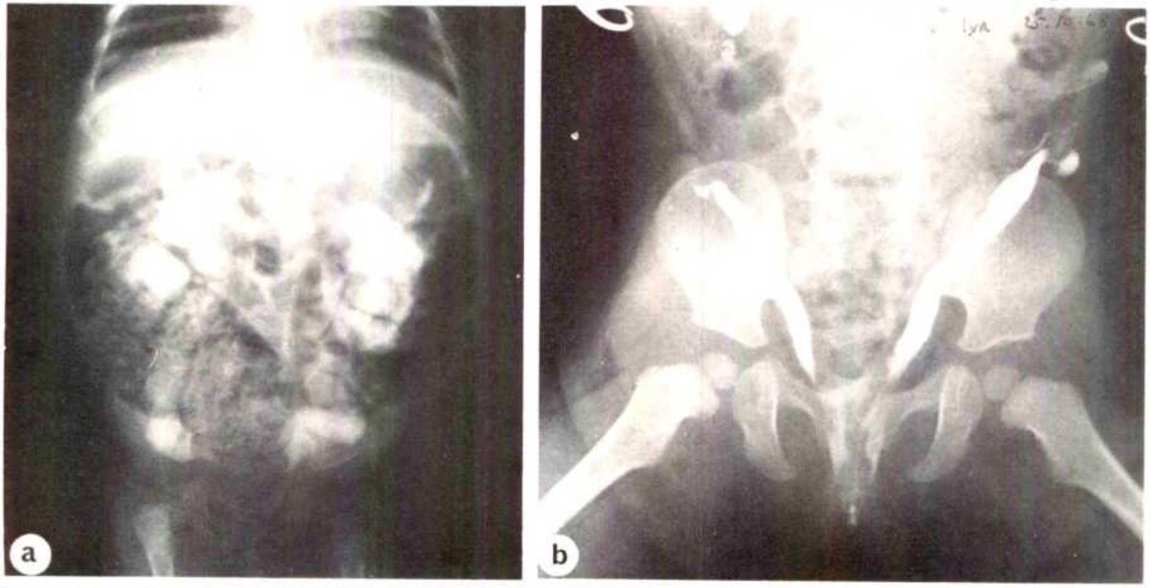


Fig. 2 (a) Excretion urogram of a girl with bilateral single ectopic ureters with distal urethral orifices, showing bilateral upper tract dilatation. The bladder did not fill with contrast medium and failed to visualise on any of the films. (b) Antegrade ureterograms in the same child, performed through loop ureterostomies. When bladder neck was occluded by an inflated Foley catheter, contrast medium flowed freely into the urethra.

in renal function was apparent on follow-up urograms.

In Group II, heminephroureterectomy was performed on the affected side in 10 children. Ureteropyelostomy was performed on the ipsilateral side in one child whose upper renal segment showed sufficient concentration on pyelography to merit preservation. Terminal ureterostomy of the duplex ureter was performed in one child with a solitary hydronephrotic duplex kidney. Implantation of the ectopic ureter into the bladder was performed in one boy. His follow-up urograms have shown deterioration of function.

Histology of 3 of the removed specimens showed renal dysplasia. All others showed changes of chronic pyelonephritis.

Complications

A temporary vesical fistula occurred in a child who had transvesical excision of the lower end of his ectopic ureter. This closed spontaneously with urethral catheterisation. One child with bilateral single ectopia developed renal stones in one of her hydronephrotic kidneys, which required nephrolithotomy. A third child required secondary excision of the residual stump of his ectopic ureter which functioned like a urethral diverticulum.

Results

Three children were lost to follow-up. One died in the neonatal period because of multiple congenital anomalies and renal failure. Nineteen children, including one girl with bilateral single ureteric ectopia, are completely continent by day. One child with myelomeningocele has a neurogenic bladder.

Three children with permanent urinary diversion have maintained satisfactory upper renal tracts. One boy, probably as a result of repeated surgery for excision of his ureteric stump, suffers from a minor degree of dampness which should improve with the development of the prostate.

Discussion

Ectopic ureter is an uncommon urological anomaly with a female predominance. The present series is unusual in that ectopia with a duplex system occurred less frequently than single ureteric ectopia, and there was a higher incidence of associated congenital anomalies in Group I than in Group II. The explanation for this is perhaps that single ureteric ectopia occurs very early in embryogenesis, for it is known that the earlier an anomaly occurs during embryogenesis, the more likely it is to be associated with multiple congenital anomalies. Bilateral single ureteric ectopia, though rare, is a well documented entity (Kjellberg *et al.*, 1957; Johnston and Davenport, 1969; Williams and Lightwood, 1972).

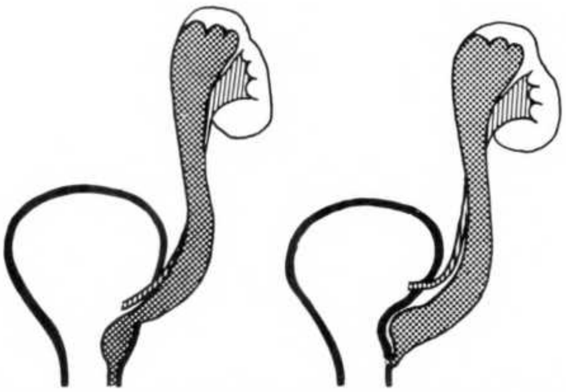


Fig. 3 The left diagram shows the anatomical disposition of an ectopic ureterocele, and the right one that of an ectopic ureter. In the case of an ectopic ureterocele the ectopic ureter to the upper moiety enters the bladder with its twin ureter through one hiatus and remains intravesical. In the case of an ectopic ureter, the dilated ureter to the upper moiety remains completely extravesical but indents the posterior bladder wall.

In an older female child whose ectopic ureter opens into the lower urethra, vestibule or vagina and whose other ureter opens into the bladder, the classical triad of continuous urinary dribbling, normal voiding and absent or impaired renal function on one side is highly suggestive of the diagnosis.

Our 3 children with bilateral single ureteric ectopia presented in the neonatal period because of associated anal anomalies. In such cases the diagnosis of ectopic ureter is overshadowed and it is only on excretion urography that it becomes apparent.

Male children with ectopic ureters do not usually present with urinary incontinence. However, the presence of epididymitis, haematuria and renal mass calls for radiographic studies, which showed an ectopic ureter in 3 of our cases.

In the female, one must scrutinise the vestibule in the region of the urethral meatus and hymen in order to locate an ectopic meatus. The presence of a duplex system with non-function or hydronephrosis of the upper hemi-kidney merits further investigations such as cystoscopy, voiding cystourethrography and retrograde pyelography. In spite of these investigations, the ectopic orifice could not be located in 18% of our cases.

On cystoscopy a dilated ectopic ureter can be mistaken for an ectopic ureterocele. With the latter, the dilated ureter from the upper hemi-kidney enters the bladder alongside the twin ureter through the same hiatus in the musculature. In contrast, a dilated ectopic ureter follows a completely extravesical course to its termination in the urethra, but often indents the posterior bladder wall to produce an endoscopic appearance closely resembling that of an ectopic ureterocele (Figs. 3 and 4). Great caution must be exercised in differentiating the 2 conditions, because if an ectopic ureter is unroofed in mistake for a ureterocele, the bladder neck will be excised and incontinence will result.

Kidneys associated with ectopic ureters, although often small, pyelonephritic or dysplastic, still retain sufficient functional tissue to produce symptoms, but fail to be visualised on routine excretion urography. In cases where there is non-visualisation of one kidney and absence of the hemitrigone, it is not only necessary to exclude renal agenesis, but also to remember the possibility of renal ectopia being associated with ectopic ureters. Arteriography is seldom helpful because of its inability to visualise the hypoplastic and poorly defined vasculature to the dysplastic kidney (Williams, 1974). The use of ^{99m}Tc-dimercaptosuccinic acid (DMSA) with a gamma camera for renal imaging has proved helpful in identifying an apparently non-functioning kidney. The marker is exclusively bound to the cortex, producing a high cortex to medulla ratio, with excretion in the urine insufficient to produce artefacts (Bingham and Maisley, 1978). The radiation dose is very small, the technique non-invasive and time-saving.

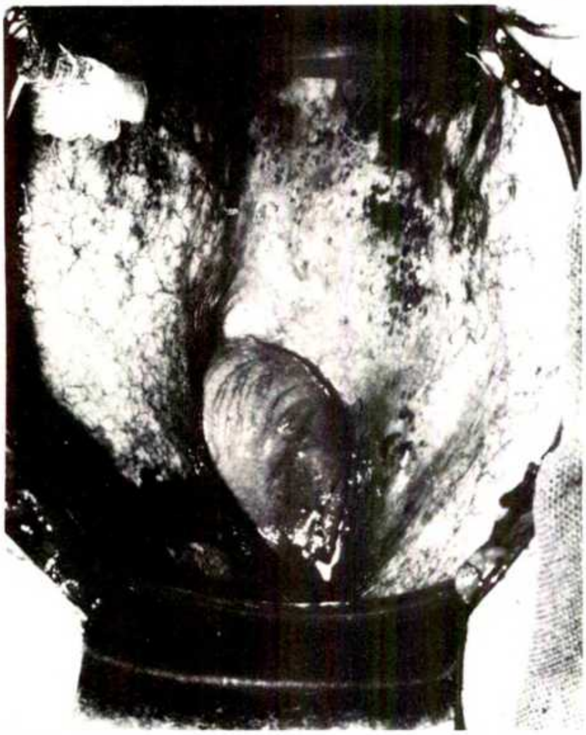
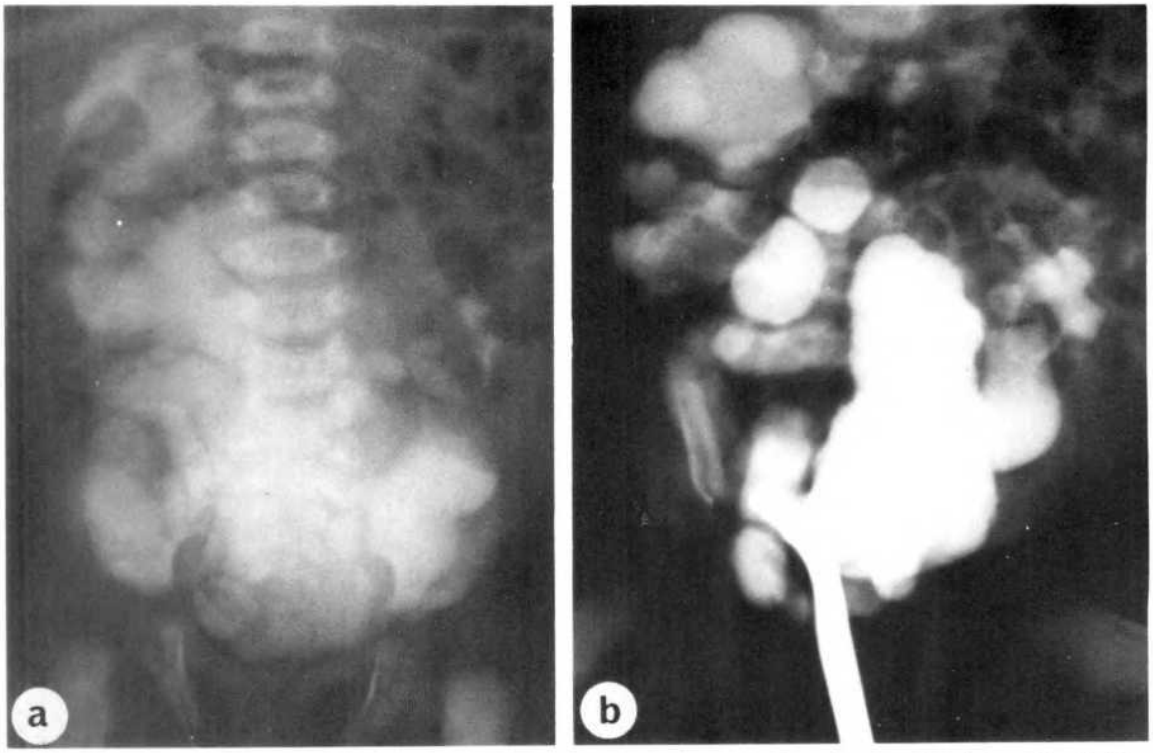


Fig. 4 Operative photograph of a child with right ectopic ureter which has projected into the bladder to produce an appearance of a ureterocele.

The treatment of ectopic ureter usually consists of nephroureterectomy or heminephroureterectomy. It is also influenced by the state of the contralateral kidney. Preservation of the ipsilateral pelvis is generally unsuccessful. In 3 cases where this was attempted by implantation of the ectopic ureter into the bladder, follow-up pyelography showed deterioration of function or no improvement.

In cases of bilateral single ectopia, the size and development of the bladder depend on the site of the ectopic orifices in the urethra. Where the ectopic orifices are situated proximal to the external sphincter, urethrovesical reflux of urine produces a bladder with some function as a reservoir. In cases of more distant ectopic ureteric orifices the bladder is an inadequate reservoir, since there has been no retrograde filling. Hutch believed that the trigonal base plate formed an essential part of the vesicourethral sphincter and was essential for continence (Hutch and Shopfner, 1968). However, this series has one girl with bilateral single ectopia who has achieved complete continence despite absence of the trigone. Both ureters opened into the proximal urethra and she had a bladder of adequate capacity; the right kidney was non-functioning and was removed. The left ureter was implanted into the bladder (Fig. 5). This case indicates that the trigonal plate is not necessary for continence.

The small size of the bladder, poor renal function and the extremely dilated ureters found in cases of bilateral single ureteric ectopia are often such that the only alternative is a permanent urinary diversion, such as ureterostomy. Gross ureteric dilatation and the presence of anal anomalies would be considered unfavourable for ureterosigmoidostomy. Ectopic ureters which allow urethroureteric reflux on voiding cystourethro-



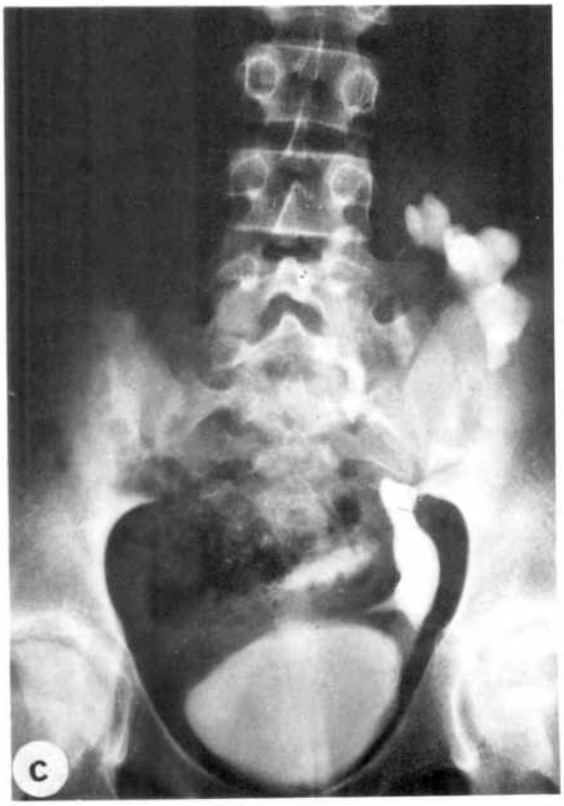


Fig. 5 (a) Excretion urogram of a baby girl with bilateral single ureteric ectopia with proximal urethral orifices, showing right hydroureteronephrosis and a left pelvic kidney with a well developed bladder. (b) Cystogram in the same child shows a well developed bladder and reflux of contrast medium into the ectopic ureters. (c) Excretion urogram of the same child 12 years later. She had a right nephroureterectomy and implantation of her left ectopic ureter into the bladder.

graphy must be removed in their entirety, even if this involves a 2-stage operation; the residual stump of such a ureter acts like a urethral diverticulum.

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The Paraureteric Diverticulum in Childhood

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Summary—The clinical features and the results of surgical treatment in 27 children with a paraureteric diverticulum treated between 1969 and 1979 were reviewed.

The condition is commoner in males. Vesicoureteric reflux and double ureters were associated findings and together with the diverticulum accounted for the high incidence of urinary infection as a presenting feature. In only 2 patients was the diverticulum seen on excretion urography, but micturating cystography confirmed the diagnosis in 24 patients.

Conservative treatment with continuous chemotherapy is satisfactory when the diverticulum is small and prior to the development of vesicoureteric reflux. In the later stages, excision of the diverticulum and reimplantation of the contiguous ureter is the surgical treatment of choice.

The existence of vesical diverticula has been known for many years and certainly there are papers written in the early years of this century describing these abnormalities and noting their association with bladder outflow obstruction (Englisch, 1904). It was pointed out that the diverticula were often paraureteric in position and could be primary rather than secondary to obstruction (Ward, 1925). For many years the aetiology remained obscure but then it was suggested that they could represent accessory ureteric buds (Joly, 1914), although no evidence was produced to support this hypothesis.

In 1952 the paraureteric diverticulum associated with vesico-ureteric reflux in children was described (Hutch, 1952). In these children there was evidence of outflow obstruction, namely bladder trabeculation.

Subsequently, paraureteric diverticula in smooth walled bladders were reported in 13 children and it was suggested that the diverticulum was an extreme form of lateral ectopia of the ureteric orifice (Johnston, 1962). Detailed descriptions of the anatomy of the trigone were then reported together with changes which occurred with growth (Hutch, 1961a and b); these changes predispose to the development of vesicoureteric reflux because of alterations in the intramural course of the ureter.

Paraureteric diverticula consist of a localised herniation through the ureteric hiatus above and lateral to the ureter. In the early stages they are intermittent, filling only when bladder pressure is high but as they increase in size, Waldeyer's sheath becomes stretched and the muscle sling is pushed downwards. Eventually the intravesical ureter becomes carried into the diverticulum and is extravesical. The vesicoureteric junction is not designed to occupy this position; it is very liable to reflux and may become obstructed. Occasionally in infants the diverticulum may cause retention of urine.

We present our clinical findings and results of surgical treatment in a series of patients seen over the 10-year period 1 April 1969 to 31 March 1979.

Patients and Methods

There were 27 patients, 20 male and 7 female. The diverticula were usually unilateral (23) with no preference for either side. The 4 patients with bilateral diverticula were boys (Table 1).

The commonest age at presentation was 4 to 7 years (17), although some presented earlier (6) and others later (4).

Table 1 Sex Ratio and Side of Diverticulum

Side of diverticulum	*Male*	*Female*	*Total*
Left	8	4	12
Right	8	3	11
Bilateral	4	0	4
Total	20	7	27

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Method of Presentation

Urinary infection, either acute or recurrent, was the commonest method of presentation (17), although on investigation a total of 23 children had infected urine. In 4 of the patients the principal symptom was enuresis, both nocturnal and diurnal. Abdominal pain (3) and haematuria (2) were other presenting symptoms and signs. One patient was diagnosed following investigation of a family with polycystic disease of the kidneys.

Radiological Investigations

In this series the standard investigations were the excretion urogram and the micturating cystogram. Only 2 diverticula were seen on excretion urography, whereas the cystogram demonstrated them in 21 patients. Repeated cystography showed diverticula in 3 further patients. Cystoscopy was necessary to make the initial diagnosis on 3 occasions. The excretion urogram did show features suggestive of vesicoureteric reflux such as upper tract dilatation (11) and renal scarring (7). In 4 patients the degree of upper tract dilatation was severe enough to be described as a megaureter. Double ureters were seen in 4 patients (Table 2).

Vesicoureteric Reflux

Twenty-four patients had vesicoureteric reflux on the same side as the diverticulum and 3 patients refluxed to the contralateral ureter. Of the 4 patients with double ureters, all refluxed to the lower pole and one to both moieties.

Surgical Treatment

Twenty-three patients were treated surgically. In all of these patients the diverticulum was excised and the ureters reimplanted by a modified Leadbetter-Politano technique. Four patients had double ureters and, in another 2, refashioning of the dilated ureter was necessary.

Table 2 Pre-operative Radiological Findings

Excretion urogram	Paraureteric diverticulum		2
	Upper tract dilatation		11
	megaureter	4	
	mild/moderate dilatation	7	
	Renal scarring		7
	Double ureters		4
Micturating cystourethrogram	Paraureteric diverticulum		24
	Initial examination	21	
	Repeat examination	3	

Medical Treatment

Four patients were treated conservatively with long term chemotherapy. In 3 of these patients the diverticula were small and not associated with reflux; the fourth patient had bilateral diverticula and developed subtotal unilateral reflux whilst under observation.

Results

The following standard protocol was used after operation. The patients were given continuous chemotherapy for a period of one month. They were then reviewed for urine outlines at 3-monthly intervals for 3 years, 4-monthly intervals for a further 3 years and then 6-monthly until 10 years from operation. Limited excretion urograms were performed at 3 months, 3 years, 6 years and 10 years. A micturating cystogram was undertaken one year after operation. The length of follow-up ranged from 1 to 9 years with a mean of 4.3 years.

Incidence of Infection

Five patients developed a confirmed urinary infection during the follow-up period. Of these, 3 had a single infection during the first year following operation, one had recurrent infection and one had asymptomatic bacteriuria.

Post-operative Radiology

The follow-up excretion urograms on those children with renal scarring showed no progressive deterioration. In patients with upper tract dilatation the radiological appearances returned to normal except in 4 cases where the dilatation was severe and, in these, clubbing of the calices remains. Post-operative cystograms reveal small residual diverticula in 2 patients.

Further Surgery

Two patients required re-operation: one patient with double ureters had persistent reflux into a lower pole ureter and the other developed contralateral reflux. A second reimplantation was successful in each case.

Discussion

The predominance of males in this series is a remarkable feature of paraureteric diverticulum,

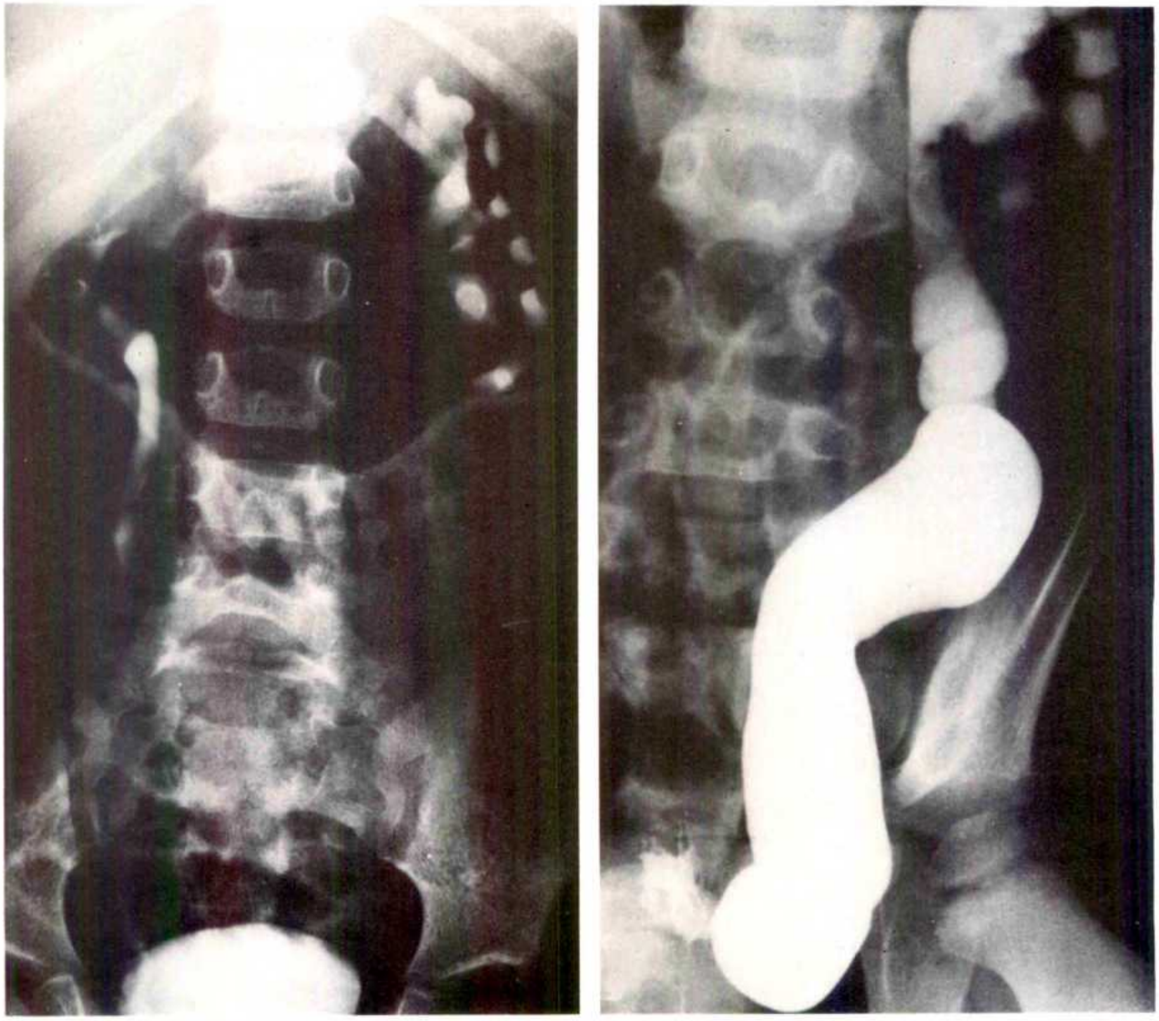

Fig. 1 (a) (left) Excretion urogram shows obstructive atrophy of the left kidney. Paraureteric diverticulum not visible. (b) (right) Micturating cystogram shows a refluxing megaureter with a paraureteric diverticulum superimposed over its lower end.

reported previously (Johnston, 1960), for which no satisfactory explanation is forthcoming. It is remarkable because the peak age at presentation of 4 to 7 years correlates well with the age at presentation of vesicoureteric reflux, which is far commoner in girls.

It is hardly surprising that urinary infection is the commonest method of presentation, for the paraureteric diverticulum predisposes to vesicoureteric reflux. Similarly, the diverticulum does appear to have a natural history, being small in the early stages but subsequently increasing in size, leading to residual urine and predisposing to infection.

Associated anomalies in our series included 4 patients with double ureters, representing a 19-fold increase over the incidence in the normal population. The significance of this finding is probably related to the method of inheritance of duplicated ureters (Whitaker and Danks, 1966; Atwell *et al.*, 1974) and to the relationship between this and the inheritance of other congenital anomalies of the urinary tract (Atwell *et al.*, 1977). There were 4 megaureters in this series but it is not possible to say whether they were primary or whether they were secondary to reflux. The diverticulum may cause mechanical obstruction to the distal ureter as well as reflux and this confuses the picture.

Diagnosis of the paraureteric diverticulum was not always easy. The failure of the excretion urogram to demonstrate the diverticulum (Figs. 1a and b) in 25 of 27 patients is an important point to remember when investigating urinary infection

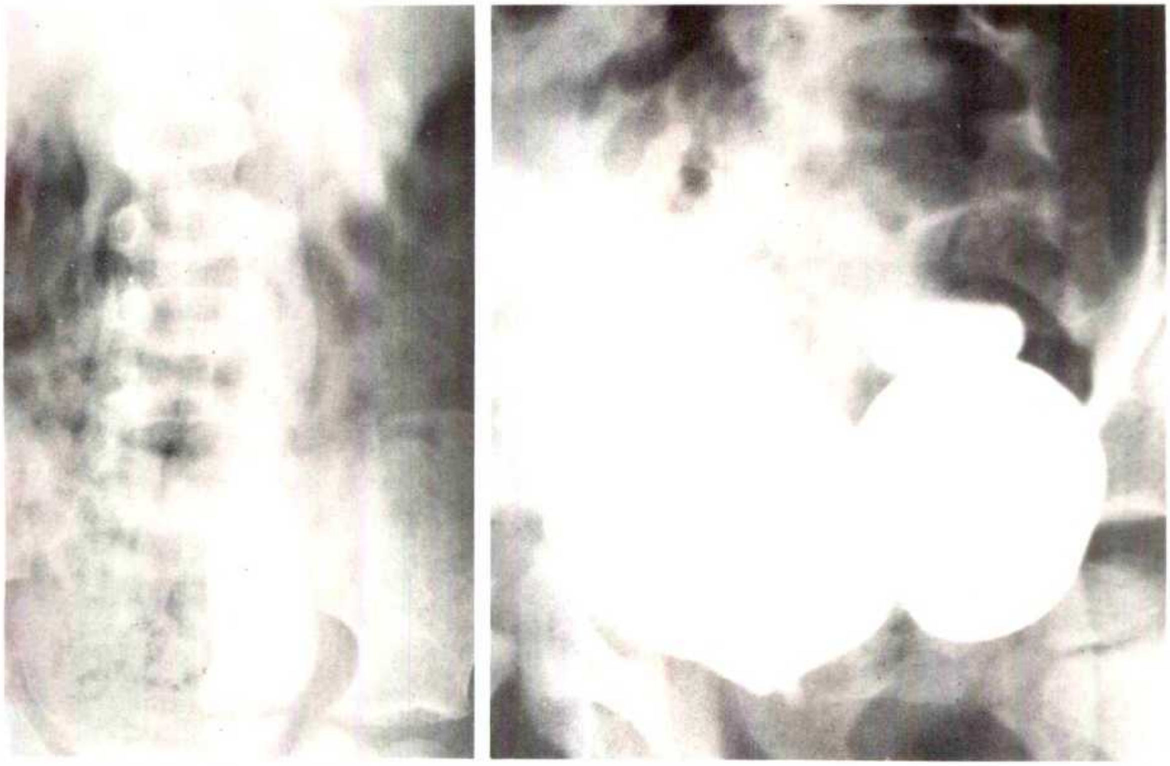

Fig. 2 (a) (left) Excretion urogram shows dilatation of the left ureter and the paraureteric diverticulum. (b) (right) Micturating cystogram showing paraureteric diverticulum and a fluid level in the adjacent megaureter.

in childhood. The presence of upper tract dilatation or renal scarring is indicative of the need for further investigation (Figs. 2a and b). The micturating cystogram is the investigation of choice and confirmed the diagnosis in 25 of 27 patients. However, it is important to remember that oblique views must be taken and screening continued during micturition because the contrast in the bladder may obscure the contrast in the diverticulum, as occurred in several of our patients (Fig. 3).

The appearances at cystoscopy are variable, depending upon the size of the diverticulum and the degree of bladder filling. Some diverticula are invisible when the bladder is empty or are represented merely by transverse mucosal wrinkles above and lateral to the ureteric orifice. The larger ones open above the ureter and, as the bladder fills, the ureteric orifice may disappear into the diverticulum. There seems no logical reason for describing small diverticula as saccules since the difference is subjective and one of degree. Lateral ectopia of the ureteric orifice is often present and taken in conjunction with the high incidence of duplication in our series reflects the relationship

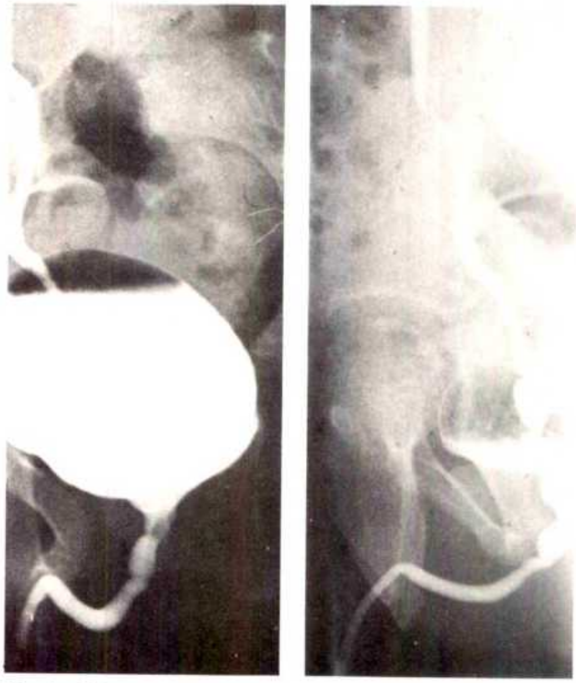

Fig. 3 Micturating cystogram revealing a hidden paraureteric diverticulum as the bladder empties.

which exists between primary reflux and duplication.

The management of paraureteric diverticulum depends upon the size of the diverticulum and its associated anomalies. Surgical treatment, which includes excision of the diverticulum and reimplantation of the ureter with or without refashioning, has been satisfactory. Excision of the diverticulum without reimplantation of the ureter has not been attempted in our series and is not recommended. There is no particular reason for using the modified Leadbetter-Politano technique other than personal preference and we have recently used advancement techniques without any difficulty. Operations on the bladder neck are not required, since there is no evidence that bladder neck dysfunction is a feature of this condition.

When the diverticulum is small, surgery can be delayed provided the effects of urinary infection are prevented by the use of continuous chemotherapy. In this way, with the help of serial radiography, it has been possible to study part of the natural history of the diverticulum and to show that some have increased in size and that this has been associated with the development of reflux.

Acknowledgement

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The Interrelationship between Paraureteric Diverticula, Vesicoureteric Reflux and Duplication of the Pelvicaliceal Collecting System: a Family Study

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Summary—The incidence of a bifid pelvicaliceal system, vesicoureteric reflux, its sequelae and paraureteric diverticulum was determined in the parents and siblings of 22 patients with a paraureteric diverticulum.

The results support the hypothesis that there is a direct genetic relationship between a paraureteric diverticulum, duplication of the pelvicaliceal system and vesicoureteric reflux. This suggests that the vesicoureteric reflux associated with a paraureteric diverticulum is primary and related to lateral ectopia of the ureteric orifice.

This syndrome complex may be inherited by multiple genes producing a cumulative effect, thus determining the length of the intravesical ureter, or by an autosomal dominant gene of variable penetrance.

Genetic factors have an important aetiological role in renal diseases such as polycystic kidneys and stones of metabolic origin. Previous investigations have established that conditions associated with infection, such as duplication of the collecting system and vesicoureteric reflux, can be inherited (Whitaker and Danks, 1966; Atwell *et al.*, 1974, 1977). A paraureteric diverticulum is an abnormality of the trigone and in a patient with such an abnormality vesicoureteric reflux or duplication may coexist or develop as a complication of the diverticulum. Apart from this association we are unaware of any reports showing that genetic factors are important in patients with a paraureteric diverticulum. The purpose of our present investigation has been to study the interrelationship between paraureteric diverticula, vesicoureteric reflux and duplication of the pelvicaliceal collecting system.

Patients and Methods

A detailed family history was obtained from the 27 index patients with a paraureteric diverticulum seen between 1 April 1969 and 31 March 1979. As 2 of the index patients were adopted and 3 others either refused or were unavailable for study, the investigation was limited to 22 index patients and their families.

Informed consent was obtained from the parents for a limited excretion urogram on themselves and on their own children. Each urogram consisted of a control film, an upper abdominal film at 10 min and a full-length film at 20 min.

In some patients with abnormal urograms further investigations were performed, such as micturating cystography and cystoscopy.

Results

Index Patients

There were 16 male and 6 female index patients. In 3 index patients (Nos. 6, 9 and 21) double or bifid ureters were found (2 bilateral, 1 unilateral). This high incidence of 13.6% contrasts markedly with the normal incidence of bifid or double ureters in the population, *i.e.* 0.7%, and represents a 19-fold increase. Vesicoureteric reflux was an extremely common finding in the index patients and was absent in only 2 patients (Nos. 16 and 17). The paraureteric diverticula were associated with megaureters in 3 index patients (Nos. 1, 2 and 5) and with an ectopic ureterocele in one index patient (No. 9).

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Table 1 Radiological Findings in the First-degree Relatives (Parents and Siblings) of Index Patients with Paraureteric Diverticula

Relationship to index patients	*Radiological findings*		
	Duplication of pelvicaliceal system	*Vesicoureteric reflux or sequelae*	*Paraureteric diverticulum*
21 fathers*	—	—	—
21 mothers†	3	1	—
32 siblings	2	2	1
74 relatives	5	3	1

* One father polycystic disease: one father renal stones.
† One mother pelviureteric junction hydronephrosis.

First-degree Relatives

In the 22 families investigated there were 77 first-degree relatives (44 parents, 33 siblings). It was possible to perform limited excretion urography in 21 fathers and 21 mothers and in 32 of the siblings—thus of the 77 relatives, 74 (96%) were investigated.

Association of Duplication of the Pelvicaliceal System in Siblings and Parents This association was found in 4 of the 22 families (Nos. 11, 14, 17 and 21). Three mothers of index patients had right bifid ureters (Nos. 11, 17 and 21) and one sister had a bifid renal pelvis (No. 14).

Association of Vesicoureteric Reflux in Siblings and Parents This association was found in 3 of the 22 families (Nos. 4, 16 and 20). One mother had bilateral reflux nephropathy (No. 4) and 2 siblings had vesicoureteric reflux (Nos. 16 and 20).

Association of Paraureteric Diverticulum in Siblings and Parents This association was seen only once (No. 4); a brother of an index patient was found to have a left paraureteric diverticulum unassociated with vesicoureteric reflux.

Association of other Renal Anomalies in Siblings and Parents Other renal anomalies were found in 3 parents, of 3 separate families: a mother

Table 2 Radiological Findings in the Siblings of the 16 Male and 6 Female Index Patients with Paraureteric Diverticula

	Radiological findings		
	Duplication of pelvicaliceal system	*Vesicoureteric reflux or sequelae*	*Paraureteric diverticulum*
24 siblings of 16 male index patients	1	1	1
8 siblings of 6 female index patients	1	1	—

Table 3 Radiological Findings in Siblings in Families with One Parent Affected and in Families with Neither Parent Affected

3 families: 1 parent affected
1 of 4 siblings affected

17 families: neither parent affected
3 of 27 siblings affected

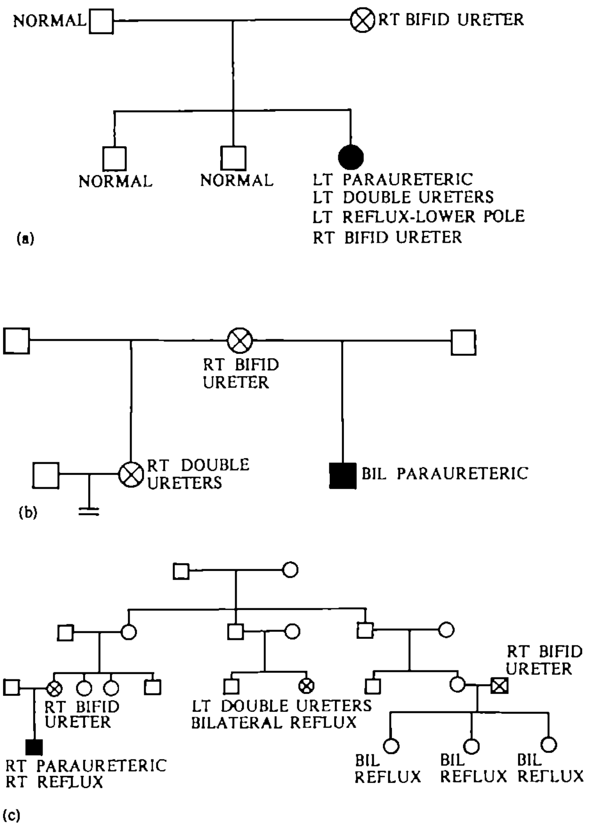

Fig. 1 Association of paraureteric diverticula with duplication. (a) Family No. 21. Paraureteric diverticulum with vesicoureteric reflux and duplication in index patient and mother. (b) Family No. 17. Bilateral paraureteric diverticula with a half-sister with double ureters and mother with a right bifid ureter. (c) Family No. 11. Paraureteric diverticulum and reflux in the index patient and duplication in the mother. Note the cousins with familial reflux.

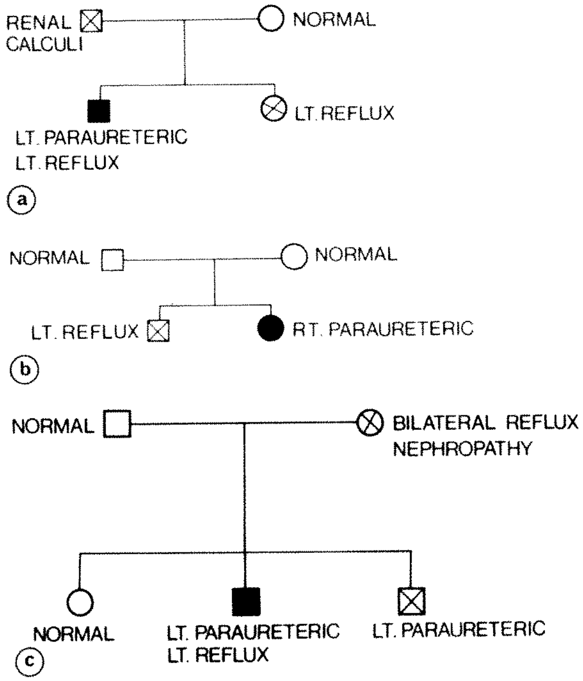

Fig. 2 Association of paraureteric diverticula with vesicoureteric reflux. (a) Family No. 20. Paraureteric diverticulum and reflux. A sister has vesicoureteric reflux. (b) Family No. 16. Paraureteric diverticulum with a brother with vesicoureteric reflux. (c) Family No. 4. Two brothers with paraureteric diverticula. Note the mother with bilateral reflux nephropathy.

with left pelviureteric junction (PUJ) hydronephrosis (No. 5), a father with polycystic kidneys (No. 19) and another father with renal stones (No. 20).

The results of the radiological investigations in these relatives showed that in 9 first-degree relatives a duplication of the pelvicaliceal system, vesicoureteric reflux or a paraureteric diverticulum were found (Table 1). There was a difference in the incidence of the radiological findings depending on whether one considered male or female index patients (Table 2). In males, 3 out of 24 (12.5%) were affected and in females, 2 out of 8 (25%) were affected. In the 20 families where urography was available for both parents there were 3 families with one affected parent and 17 families with neither parent affected. In the former group, one of 4 siblings was found to have a bifid pelvicaliceal system, vesicoureteric reflux or a paraureteric diverticulum. In the latter group, 3 of the 27 siblings were similarly affected (Table 3).

The association of a paraureteric diverticulum with a duplex urinary tract is seen in Figures 1a, b and c. Similarly, the association with vesicoureteric reflux is shown in Figures 2a, b and c. In particular, the family seen in Figure 1c shows the interrelationship which exists between duplication, vesicoureteric reflux and paraureteric diverticula. In one family (Fig. 1) the index patient had bilateral paraureteric diverticula but his half-sister by his mother's first marriage had double ureters.

In 7 of the 22 families investigated we found either duplication, reflux or a paraureteric diverticulum in first-degree relatives. Full details of each family are given in the Appendix.

Discussion

As only one first-degree relative with a paraureteric diverticulum was found in this investigation, it seems unlikely that such diverticula are inherited as a single entity. It is difficult, however, to compare the incidence of 1 in 74 with that found in the normal population, since there are no existing data with which to make a relevant comparison.

The high incidence of duplication of the urinary tract in both the index patients and first-degree relatives suggests a direct relationship between the 2 conditions. The incidence in the index patients of 3 in 22 patients represents a 19-fold increase in the expected incidence of 0.7 per 100 patients. As duplication of the urinary tract is inherited (Whitaker and Danks, 1966; Atwell *et al.*, 1974), one would expect to find a higher incidence in the first-degree relatives in this series. However, duplication was found in only one of these initial families (No. 21) but further evidence of duplication was found in 3 other families as a result of the survey (Nos. 11, 14, 17), *i.e.* 4 new patients with duplication were found in new families or 5 out of the 74 relatives examined, an incidence of 6.6% or nearly a 10-fold increase over the expected.

The association between duplication of the pelvicaliceal system and vesicoureteric reflux has previously been reported (Atwell *et al.*, 1977) and, in our series, 3 patients were found with evidence of reflux or its sequelae such as reflux nephropathy. The true incidence may be greater than this since not all of the patients were subjected to a micturating cystogram, this investigation being performed only if the results of the urogram or the history suggested that further investigations were indicated. If one accepts that paraureteric diverticula, vesicoureteric reflux and

Appendix Details of Patients and Families

Family no. and sex of index patient	*Index patient*	*Parents*		*Siblings*	*Remarks*
		Father	*Mother*		
1. (M)	Left paraureteric Left reflux Left megaureter	NAD	NAD	2 sisters, NAD	
2. (M)	Left paraureteric Left reflux Left megaureter	NAD	NAD	2 brothers, NAD	
3. (M)	Right paraureteric Bilateral reflux	NAD	NAD	1 brother, NAD 1 sister, NAD	
4. (M)	Left paraureteric Left reflux	NAD	Bilateral reflux nephropathy	1 brother Left paraureteric 1 sister, NAD	
5. (M)	Left paraureteric Left reflux Left megaureter	NAD	Left PUJ hydronephrosis	2 brothers, NAD 2 sisters, NAD	
6. (F)	Left paraureteric Left double ureters Left reflux	NAD	No EU	No siblings	Mother allergic to iodine
7. (M)	Bilateral paraureteric Left reflux	NAD	NAD	1 brother, NAD	
8. (M)	Bilateral paraureteric Bilateral reflux	NAD	NAD	1 brother, NAD	
9. (M)	Right paraureteric Bilateral double ureters Bilateral reflux Right ecoptic ureterocele	NAD	NAD	1 sister, NAD	
10. (M)	Right paraureteric Right reflux	NAD	NAD	3 sisters, NAD	
11. (M)	Right paraureteric Right reflux	NAD	Right bifid ureter	No siblings	Cousins with familial reflux
12. (F)	Left paraureteric Left reflux	NAD	NAD	1 brother, NAD	
13. (M)	Left paraureteric Left reflux	NAD	NAD	1 brother, NAD	
14. (F)	Right paraureteric Right reflux	NAD	NAD	1 brother, NAD 1 sister, bifid renal pelvis 1 sister, no EU	
15. (M)	Right paraureteric Right reflux	NAD	NAD	No siblings	
16. (F)	Right paraureteric	NAD	NAD	1 brother, reflux	
17. (M)	Bilateral paraureteric	No EU	Right bifid ureter	1 half-sister, double ureters	
18. (F)	Right paraureteric Bilateral reflux	NAD	NAD	1 brother, NAD 1 sister, NAD	
19. (M)	Bilateral paraureteric Bilateral reflux	Polycystic kidneys .	NAD	2 brothers, NAD	Familial polycystic kidneys
20. (M)	Left paraureteric Left reflux	Renal stones	NAD	1 sister, reflux	
21. (F)	Left paraureteric Left double ureters Right bifid ureter Left reflux	NAD	Right bifid ureter	2 brothers, NAD	
22. (M)	Left paraureteric Left reflux	NAD	NAD	1 brother, NAD	

M = Male.
F = Female.
EU = Excretion urogram.

duplication are interrelated, the incidence in first-degree relatives was 9 in 74 (12.1%), which closely approximates to the increased incidence of duplication in the index patients of 3 in 22 patients (17-fold increase: 19-fold increase).

It has been suggested that a paraureteric diverticulum represents an aborted ureteric bud (Joly, 1914). The vesicoureteric reflux associated with paraureteric diverticula could be either primary or secondary and may be related to lateral ectopia of the ureteric orifice (Lyon *et al.*, 1969; Cass and Ireland, 1972). Our evidence would support either of these hypotheses and indeed they are not mutually exclusive.

The only satisfactory explanation for lateral ectopia of the ureteric orifice is faulty development and it is probably due to early separation of the ureteric bud from the mesonephric duct, resulting in weak attachment to the trigone. It has been suggested that this is genetically determined; this may be either polygenic (Burger, 1972) or transmitted as an autosomal dominant gene of variable penetrance (Whitaker and Danks, 1966; Atwell *et al.*, 1974). Duplication is due either to bifurcation of the ureteric bud or to the formation of 2 separate ureteric buds on the mesonephric duct; the most caudal of these is taken up into the bladder first and is liable to early separation from the mesonephric duct, resulting in lateral ectopia.

The exact mechanism for the formation of a paraureteric diverticulum is not quite clear, but it seems likely that faulty attachment of the ureteric bud to the trigone results in a weakness which becomes everted by the normal intravesical pressure, forming a diverticulum. We have shown in our series a high incidence of duplication, vesicoureteric reflux and paraureteric diverticulum in the first-degree relatives of index patients, which strongly suggests that these 3 conditions are part of a syndrome complex and that the mechanism of inheritance is similar.

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Hypokalaemic Hyperchloraemic Metabolic Acidosis and Vesical Stone Complicating Appendicovesical Fistulae

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Summary—Two patients with appendicovesical fistulae are described. Both presented with gastrointestinal and urinary symptoms. Biochemical examination showed hypokalaemic hyperchloraemic metabolic acidosis; radiographic investigations showed a vesical stone and a communication between the bladder and the bowel. The findings at operation suggested that the fistulae may have arisen as complications of previous appendicitis. The diagnosis of appendicovesical fistulae may be difficult but should be considered in the presence of hypokalaemic hyperchloraemic metabolic acidosis and vesical stones.

Fistulous tracts between the appendix and urinary bladder are uncommon but often arise as a complication of appendicitis (Forbes and Rose, 1964; Di Paola and Stockwell, 1976; Eickhoff, 1976; Woods and Gowin, 1978). Diagnosis may be difficult, for the majority present only with recurrent urinary tract infections (Eickhoff, 1976). There has been no detailed report of electrolyte disorders in appendicovesical fistulae and this is in contrast with patients who have undergone an elective urinary diversion procedure, such as ureterocolic anastomosis, in whom hypokalaemic hyperchloraemic acidosis has been extensively recorded (Jacobs and Stirling, 1952; Parsons *et al.*, 1952). We report this complication in 2 patients with an appendicovesical fistula, each of whom had a large vesical stone. The investigation and management of these patients is described and the mechanism of the electrolyte disorder is discussed.

Patients

Case 1. This 22-year-old welder presented with a 3-month history of weight loss, nausea, diarrhoea and depression. For 2 months he had noted a gradual decrease in urine volume. There was no significant past medical history. On examination he looked wasted and dehydrated. No other abnormality was noted. His blood pressure was 140/70 mmHg, pulse rate 100/min and respiratory rate 26/min. The urine contained albumin but no glucose. The clinical findings, together with the admission blood biochemistry (Table), indicated dehydration, uraemia and severe hypokalaemic hyperchloraemic metabolic acidosis.

Initial management consisted of rehydration and correction of the electrolyte disorder with intravenous molar lactate (3 l/24 h) containing potassium supplements (100 mmol/24 h). His clinical condition improved, the urine volume increased and the blood biochemistry slowly reverted to normal. Further investigations were then performed. A plain abdominal film showed a large solitary vesical stone. A midstream urine specimen taken on admission resulted in a pure growth of *Escherichia coli*. An intravenous urogram showed bilateral distension of the pelvicaliceal systems down to the vesicoureteric junction. The urinary bladder was of small capacity and contained a large laminated stone. The wall of the bladder was thick and irregular. There appeared to be a fistulous tract between the right side of the bladder and the ileum which was seen on both a cystogram and a barium meal with follow-through examination. No radiographic abnormalities of the ileum were noted and a barium enema showed no evidence of colitis.

Table Admission Blood Biochemistry and Haematology Levels

	Case 1	*Case 2*	*Normal range*
Urea (mmol/l)	27	53	3.0-7.5
Creatinine (mmol/l)	0.12	0.43	0.07-0.14
Bicarbonate (mmol/l)	10	5.5	24-32
Potassium (mmol/l)	2.1	3.3	3.5-5.0
Sodium (mmol/l)	136	142	135-143
Chloride (mmol/l)	113	122	95-105
Haemoglobin (g/dl)	10.3	9.3	
White cell count (× 10^9/l)	14.1	14.9	

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By the fifth day the patient felt very much better. His blood biochemistry was normal (blood urea 3 mmol/l, bicarbonate 25 mmol/l, chloride 105 mmol/l, potassium 4.4 mmol/l, sodium 135 mmol/l). It was therefore decided to proceed to laparotomy, at which the appendix and a small loop of terminal ileum were found adherent to the bladder. There was a fistulous tract between the bladder and the appendix. An appendicectomy was carried out, the fistulous tract excised and the vesical stone removed. Examination of the appendix showed areas of mucosal congestion and histology indicated submucosal fibrosis. The stone was laminated and within it lay what appeared to be the tip of the appendix. This was confirmed histologically. There was also partially calcified amorphous material within the stone which, on histology, appeared to contain remnants of plant cell walls.

The patient made an uneventful recovery after the operation. He maintained a good urine output and had no further diarrhoea. His blood biochemistry remained normal and on discharge his urine was sterile. On follow-up 3 months later he maintained that he felt fine and was managing well at work. There was no biochemical evidence of impaired renal function and the urine remained sterile.

Case 2. This 28-year-old male insurance clerk presented with a 10-day history of malaise, sore throat, headaches, pyrexia and rigors. On the evening prior to admission he appeared withdrawn, had watery diarrhoea and began to breathe deeply and laboriously. He was anorexic, felt thirsty and drank excessive quantities of water. He felt drowsy on the morning of admission. There was no previous medical history except for vague depression and lassitude for about 2 years.

On examination he was pale, dehydrated and febrile (38°C). He had Kussmaul respiration (rate 32/min), a dry tongue and a uraemic fetor to his breath. His blood pressure was 140/75 mmHg and pulse rate was 110/min. He was drowsy and responded to commands with difficulty. There were no abnormalities in the chest and abdomen and no localising neurological signs. The admission blood biochemistry indicated uraemia and severe hyperchloraemic metabolic acidosis with hypokalaemia (Table). Arterial blood hydrogen ion activity was 86 nmol (normal = 36 to 44 nmol), pCO_2 1.43 kPa (normal 4.5—6.8 kPa), and pO_2 17.5 kPa (normal 12-15 kPa). Standard bicarbonate was 5.2 mmol/l and base excess —25 mmol/l.

Initial management consisted of correcting dehydration, hypokalaemic metabolic acidosis and uraemia. He was therefore given 1.4% sodium bicarbonate and isotonic saline intravenously. Peritoneal dialysis was commenced with Hartmann's solution (sodium 131, potassium 5, chloride 111, lactate 29 mmol/l). Although the admission potassium level was 3.3 mmol/l, and just below the lower limit of the normal range of 3.5 to 5.0 mmol/l, it was felt that the potassium deficit was masked by severe dehydration. A further 2 mmol/l of potassium chloride was therefore added to each litre of dialysate. The patient was initially oliguric and was therefore catheterised. He also had diarrhoea and it was noted that, in spite of rehydration, there was no increase in urine volume. The diarrhoea coincidentally became more profuse. However, he gradually felt better and a plain abdominal film then showed a large solitary vesical stone (Fig. 1). A specimen of urine obtained when the patient was first catheterised resulted in a pure growth of *Pseudomonas aeruginosa*.

The patient gradually improved, although the diarrhoea continued unabated despite the addition of anti-diarrhoeal agents. After 5 days of peritoneal dialysis the urea had come down to 30 mmol/l. Potassium was 4.2 mmol/l, sodium 135 mmol/l, CO_2 18 mmol/l and chloride 106 mmol/l. In view of the radiological findings it was decided to proceed initially to cystoscopy under general anaesthesia. No evidence of urethral obstruction was found and the bladder contained 15 ml of foul blood-stained urine. The bladder wall was irregular and oedematous with marked thickening on

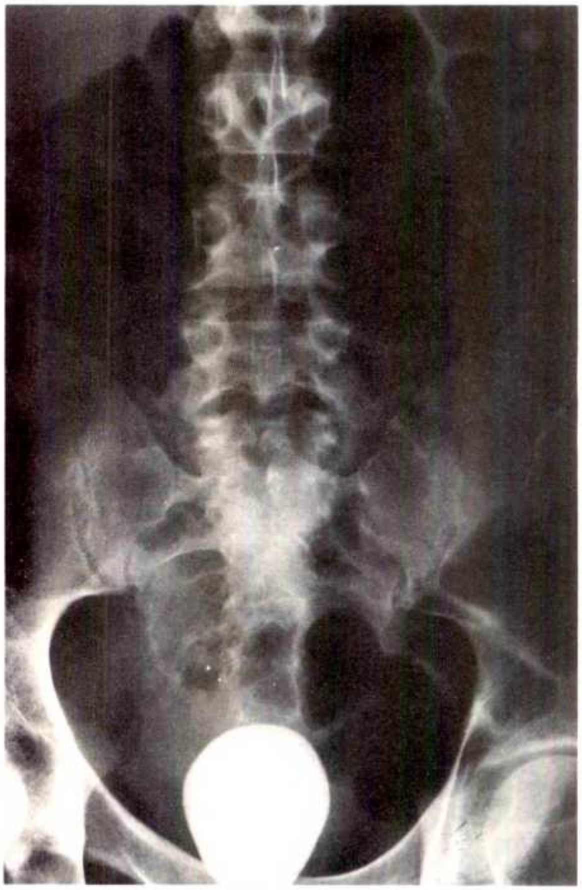

Fig. 1 Case 2. Plain X-ray of abdomen showing solitary large vesical stone.

the right. Irrigation of the bladder resulted in fluid emerging from the rectum and suggested a vesicorectal fistula. It was, however, felt important to proceed to cystolithotomy before investigating this further. The stone was therefore removed through an abdominal incision and an indwelling Foley catheter inserted. The stone consisted of a larger, outer part which was hard and grey and a smaller, inner section which was soft and brown (Fig. 2). The outer part weighed 81 g and contained 17% calcium, 3.3% magnesium, 2.1% oxalate, 11.8% phosphate and 1.7% ammonium. The inner section weighed 2 g, and contained 23.5% calcium, 1.1% magnesium, 3.8% oxalate, 11.7% phosphate and 0.1% ammonium.

Post-operatively the patient had a massive 5-litre diuresis in the first 24 h. Adequate hydration was maintained and his blood biochemistry improved spontaneously. No further dialysis was needed. By the tenth post-operative day the urea was 9.8 mmol/l, CO_2 19 mmol/l, chloride 108 mmol/l and creatinine 0.25 mmol/l. The potassium and sodium were normal. Investigations into a possible vesicorectal fistula then proceeded. A micturating cystogram strongly suggested a vesicocaecal fistula (Fig. 3).

At laparotomy a week later, when the patient felt well and when his blood biochemistry was normal, a fistula tracking from the appendix to the urinary bladder was demonstrated. The caecum was dissected free, an appendicectomy was carried out and the base of the appendix and the opening of the bladder were closed. The serosa of the appendix was found to be thickened but not hyperaemic. The lumen was obliterated and histology showed non-specific chronic inflammation and fibrosis.

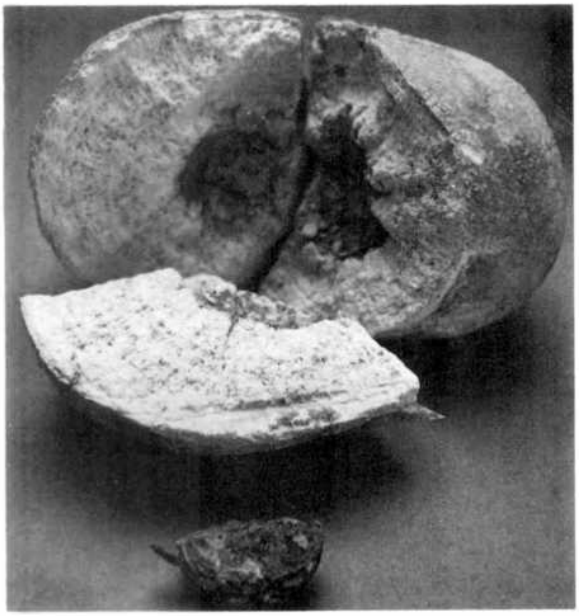

Fig. 2 Case 2. Stone removed from bladder and cut to show outer and inner components.

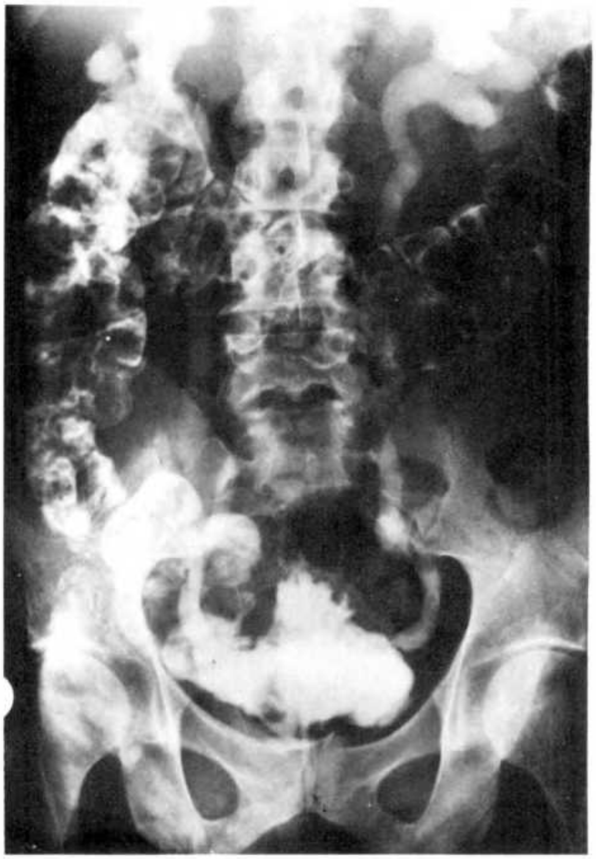

Fig. 3 Case 2. Micturating cystogram. There is bilateral vesicoureteric reflux into dilated renal collecting systems and ureters. Contrast also passed freely from the right side of the bladder into the lower pole of the caecum through a fistulous tract.

The patient recovered uneventfully from this operation. Renal function remained biochemically within normal limits and his urine was sterile. This remains so 8 months later with the patient feeling well and back to full-time work. An intravenous urogram, however, continues to show some dilatation of the pelvicaliceal systems and ureters.

Discussion

Appendicovesical fistulae account for about 5% of all enterovesical fistulae. The majority of patients are between 10 and 40 years of age (Parton, 1958; Eickhoff, 1976). Fistulae are 5 times more common in men and this may be because in women the internal genital organs form a barrier between the gut and the bladder (Mayo and Blunt, 1950). In most patients there is no previous history of appendicitis (Eickhoff, 1976). Neither of our patients admitted to symptoms to suggest this, although histopathology of the removed appendices indicated chronic inflammatory changes and fibrosis.

Both of our patients presented with a history of anorexia, increased thirst, polydipsia, nausea, vomiting, diarrhoea and malaise. On admission they were dehydrated and had a severe metabolic acidosis with hypokalaemia and hyperchloraemia. Other than a scanty reference to a solitary patient with an appendicovesical fistula, in whom "blood studies revealed a slightly elevated output of blood urea nitrogen and hyperchloraemic acidosis" (Jaffe and Evans, 1964), we have been unable to find a description of the electrolyte disorders in patients with appendicovesical fistulae. In patients with ureterosigmoidostomies, however, hypokalaemic hyperchloraemic metabolic acidosis has often been reported. In such patients, pooling of urine in the colon results in 2 physiological events which tend to produce metabolic acidosis: movement of bicarbonate from plasma to urine in exchange for chloride, and absorption of urinary ammonium from the bowel (Parsons *et al.*, 1952; Boyce and Vest, 1952). The former reduces plasma bicarbonate concentration and the latter results in the addition of hydrogen ions to body fluids, both of which contribute to metabolic acidosis. Hyperchloraemia occurs because the reabsorption of chloride is slightly greater than that of sodium (Parsons *et al.*, 1952). Polyvalent ions such as sulphates and phosphates, which are normally present in urine, also increase chloride reabsorption and, furthermore, the fluid compartment in which chloride is diluted following reabsorption is approximately seven-tenths that of sodium (Pyrah *et al.*, 1955). The kidney may adequately compensate by increasing acid excretion, but the longer urine is in contact with the colonic mucosa the greater are the exchanges, and this proportionately increases the compensatory load on the kidney (Christy, 1975). Impairment of renal function, therefore, may result in severe hyperchloraemic metabolic acidosis. In both of our patients a combination of infection, reflux and dehydration may have resulted in impaired renal function and in the severe metabolic upset. It is to be noted that, in animals, diversion of the total urine output into the ileocaecal region results in uraemia, severe metabolic acidosis and often death (Geer and Dragstedt, 1938; Boyce and Vest, 1952), while in man severe biochemical imbalance follows implantation of the right ureter into the caecum and the left ureter into the sigmoid colon (Kekwick *et al.*, 1951). The situation described above may be analogous to what we observed in our 2 patients.

Both of our patients were hypokalaemic on admission, the second being apparently less so, but this was probably because the potassium deficit was masked by severe dehydration. Hypokalaemia has also been described in patients with ureterocolic anastomoses (Parsons *et al.*, 1952; Sataline and Simonelli, 1961). Renal tubular dysfunction following repeated bouts of pyelonephritis, secondary to colonic organisms ascending the ureter, may be one cause, as it leads to potassium wasting. Potassium and bicarbonate ions are also secreted by the colonic mucosa to replace sodium and chloride ions which are reabsorbed from the urine (Stamey, 1956). Potassium loss is probably a protective mechanism whereby the severity of the acidosis is reduced. Because potassium and hydrogen ions compete for the same cellular enzyme system (Berliner *et al.*, 1951), an increase in one may produce a decrease in the other. Hypokalaemia may impair renal concentrating power and result in polyuria and dehydration (Relman and Swartz, 1958).

The management of the electrolyte disorders in these patients consists of a combination of rehydration and replacement of bicarbonate as a bicarbonate solution. It is important to correct the potassium deficit in these patients since correction of the acidosis will cause the movement of this ion from the intravascular to the cellular compartment and a further fall in serum potassium. Frequent electrolyte measurements may be needed in the initial stages. Dialysis, as in patient 2, may be necessary to overcome the severe acidosis and uraemia which may occur.

There may be few urinary symptoms associated with appendicovesical fistulae, unlike vesicocolic fistulae in which faecaluria and pneumaturia are common. These symptoms have been reported only in appendicovesical fistulae resulting from a periappendicular abscess where the communication between the bladder and the appendix was large (Eickhoff, 1976). Chronic bacteriuria occurs in half of the cases with appendicovesical fistulae (Jaffe and Evans, 1964). Most infections are caused by a pure bacterial growth rather than a mixture of bacterial organisms (Carson *et al.*, 1978). In each of our patients, urine culture resulted in a pure growth of *Pseudomonas aeruginosa* and *Escherichia coli.*

Vesical stones have been reported in approximately 50% of cases of appendicovesical fistulae (Parton, 1958). The initial causative factor may be either an organic nucleus (food, seed or faecolith) from the bowel or chronic infection (Williams and Prien, 1978). In previous cases, the composition of the stones was not stated and it is therefore impossible to ascertain what the precipitating or the perpetuating causes were. In Case 1, the tip of the appendix lay in the middle of the stone and this strongly suggests that it was the nucleus for the formation of the stone. It is likely, however, that chronic infection contributed to its growth. In Case 2, analysis of the stone indicated that it was of mixed phosphate variety and this strongly suggests that it resulted from chronic infection.

Both of our patients had bilateral distension of the pelvicaliceal systems and ureters. This has been observed in patients with ureterocolic anastomosis (Parsons *et al.*, 1952). Some authors have claimed that obstruction is the most likely cause (Grey Turner and Saint, 1936) although others have drawn attention to the fact that the urinary bladder normally has a lower resting pressure than the rectum and colon and this may therefore be contributory (Boyce and Vest, 1952).

In our patients it is likely that the stones or the associated reaction of the mucosa and ureteric orifices resulted in obstruction and the bilateral distension of the pelvicaliceal systems and ureters. This is supported by the fact that removal of the stone in Case 2 was followed by a massive post-obstructive diuresis.

The diagnosis of appendicovesical fistulae may be difficult. It is reported that cystoscopy may help in 40% of cases and the use of contrast media during cystography and barium meal or a barium enema may provide a diagnosis in 50% (Gross and Peng, 1969). In both of our patients the use of contrast media, either in the bladder or in the bowel, confirmed the diagnosis. When our patients presented, both had gastrointestinal and urinary symptoms and severe hypokalaemic hyperchloraemic metabolic acidosis. The presence of a vesical stone in each case provided a further clue to the aetiology of the condition and we therefore suggest that, although uncommon, a diagnosis of appendicovesical fistula be considered in patients with this combination of findings.

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Ileal Loop Replacement and Restoration of Kidney Function in Extensive Bilharziasis of the Ureter

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Summary—Ileal loop replacement is often the only possible treatment for extensive bilharziasis of the ureter. Experience with 5 such cases is presented and the special problems arising from the nature and extent of the lesion are discussed.

In bilateral cases, attempts should be made to preserve as much renal tissue as possible. Non-functioning kidneys in 3 cases were not removed and a degree of function was restored following the relief of obstruction by also connecting these kidneys to the ileal loop.

Bilharziasis of the ureter is a difficult condition to treat. This disease frequently causes extensive bilateral ureteric obstruction with resulting renal damage. The obstruction may be due not only to the strictures themselves, but also to the adhesions and periureteritis which produce tortuosity and kinking. Calcification of the ureteric wall or extensive replacement of its muscle layer by the bilharzial lesions may lead to obstruction even in the absence of stones or strictures. Treatment by measures such as ureteric dilatation (open or closed) or resection and end-to-end anastomosis do not usually give good results. On the other hand, operations such as reflux-preventing ureteroneocystostomy or Boari flap procedures are not suitable because of the associated bladder disease. This paper aims at emphasising the role of ileal loop replacement in the treatment of extensive ureteric bilharzial disease.

Patients and Methods

Case 1. A.I.H., a 22-year-old man, presented with bilateral ureteric fistulae and very poor general condition. He gave a history of bilateral ureterolysis, ureterolithotomy and open dilatation of the bilharzial strictures. Excretion urography showed bilateral gross hydronephrosis and hydroureter down to the sites of the fistulae. Cystoscopy confirmed bilharziasis. Two months later his left fistula dried up. Loss of left renal function was suspected and confirmed radiologically. After extensive supportive treatment, an ileal loop ureteric replacement was performed as in Figure 1.

Case 2. R.A., a very ill 22-year-old man, presented with a tense mass in the abdomen 2 weeks after a left ureterolithotomy with open dilatation of a lower ureteric bilharzial stricture. A fluid mass was drained. Subsequently an excretion urogram showed gross hydronephrosis and hydroureter down to a stricture which was higher than that initially encountered. An ileal loop replacement was carried out.

Case 3. B.A., a 50-year-old man, presented with recurrent attacks of left renal colic and increasing dysuria. An excretion urogram showed calcification of the bladder and lower third of the ureters, with non-function of the right kidney and left-sided hydronephrosis with hydroureter down to the strictured and

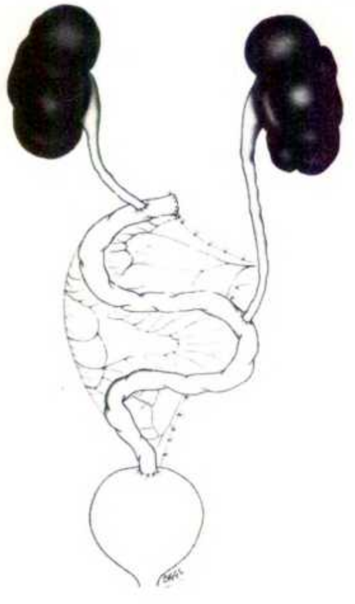

Fig. 1

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calcified lower ureter. Cystoscopy showed a bilharzial bladder, and a transurethral resection was done to relieve dysuria. Later an ileal loop replacement was carried out, as in Figure 2, together with removal of a left lower pole stone.

Case 4. J.A., a 27-year-old man, presented with an attack of left renal colic. He gave a past history of urinary bilharziasis. Excretion urography showed a calcified bladder, non-functioning right kidney and gross left-sided hydronephrosis and hydroureter. The lower third of the ureter did not fill. An ileal loop replacement of the strictured parts of his ureter was performed as in Figure 3.

Case 5. H.S., a 35-year-old man, presented with a left post-operative urinary fistula. The nature of the operation carried out 2 months previously was not known, although he had a past history of bilharziasis. An excretion urogram showed right hydronephrosis and hydroureter. The lower third of the ureter was not seen. A similar picture was seen on the left side, only the upper 2.5 cm of the ureter filling with contrast media. Ileal loop replacement of the strictured ureters was carried out (Fig. 4).

Points of Technique

A neomycin bowel preparation was used in all cases.

A long midline incision from xiphisternum to symphysis pubis gave adequate exposure, allowing high procedures such as nephrolithotomy or pelvi-ileal anastomosis to be performed with ease. The contents of the isolated loop were squeezed out and an isoperistaltic anastomosis was performed in unilateral cases. In bilateral disease a twisting loop, as in Figures 1, 2, 3 and 4, was used without compromising the blood supply to the loop in any case.

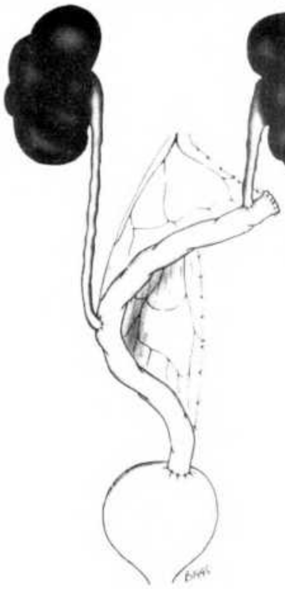

Fig. 2.

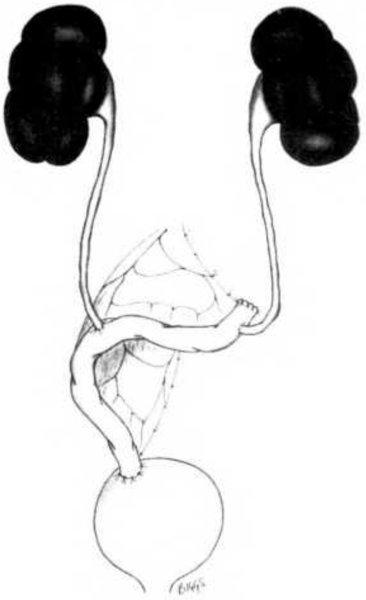

Fig. 3

In patient 5 the end of the ileum was anastomosed to the front of the left pelvis (Fig. 4). In the remaining patients the proximal end of the loop was closed and a direct uretero-ileal anastomosis, as in Figures 1, 2 and 3, was performed.

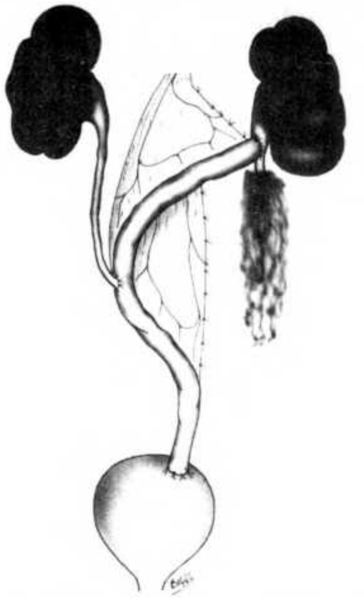

Fig. 4 a—Area of dense fibrosis due to peri-ureteritis and extravasation.

The bladder was opened on the right posterolateral surface sufficiently to examine the bladder and deal with any coexisting bladder neck obstruction. Anastomosis of the distal end of the loop was carried out to this opening from outside the bladder.

Except in Case 1, fine Portex tubing splints were used for the anastomosis bringing the end of the tube through the bladder and abdominal wall. Two such tubes were used for bilateral cases. The diseased lower segment of ureter was left *in situ*.

Results

Case 1, in which no splints were used, was the only case with a stormy post-operative period. He developed gram-negative septicaemia and ileus after leaking infected urine into the peritoneal cavity on the second day. He responded well, however, to conservative therapy.

The remaining patients had an uneventful post-operative period. Splints were removed after 7 to 10 days, the urethral catheter being kept a few days longer.

During the first 2 weeks a considerable amount of mucus was passed in the urine and the patients had frequency of micturition both by day and night. This gradually ceased.

Case 4 returned to hospital 2 weeks after discharge with acidosis following a heavy protein intake. His bladder was empty and there was no apparent stasis in the loop. Parenteral fluids corrected his acidosis. In this series of 5 cases there was no post-operative mechanical intestinal obstruction and no persistent fistula. There was no mortality.

Case 1 lost function to the left kidney while awaiting ileal loop replacement. Two other patients had a non-functioning kidney on admission. All of these kidneys were found to be grossly hydronephrotic. The ureters were divided high up and connected to the ileal loop instead of performing a nephrectomy. An excretion urogram 1 to 2 months post-operatively confirmed restoration of function, although in Case 4 this was only demonstrable on the 12-h film.

Discussion

Although the technique of ileal loop replacement of the ureter has been described before (Goodwin, 1960; Macalister, 1960; Amin, 1976), it has not yet gained widespread recognition. Badr (1977), in a chapter on the surgical management of urinary bilharziasis, did not mention ileal loop replacement as a possible line of treatment.

Honey and Gelfand (1960) employed a length of isolated ileum to replace the diseased lower ureter when they found a bladder flap impossible. Weinberg (1970) had disastrous results following flap procedures for bilharziasis and reported 4 other cases managed by loop replacement. Ghoneim *et al.* (1971) used similar techniques in 4 out of 19 survivors in a series of 21 patients admitted with anaemia due to bilharzial strictures of the ureter. Amin (1976) reported 18 cases of ileal loop replacement. Half of these patients had bilateral fibrosis of the lower ureter.

Although it has been recommended that the isolated loop should be irrigated during surgery by saline (Macalister, 1960) or a warm solution of neomycin (Goodwin, 1960), this was found to be unnecessary. It seems clear from a report by Davis and Nealon (1957), and from Goodwin's experience (1974), that replacement of the ureter by small intestine should always be performed in an isoperistaltic direction. In right-sided and bilateral cases a twisting type of rotation of the isolated loop is necessary to achieve this. Weinberg (1970) noticed that the loop became cyanotic when placed isoperistaltically on the right side, but became viable in the antiperistaltic position. This observation led Amin (1976) to lay the isolated loop in a U-shaped arrangement, giving an isoperistaltic anastomosis on the left side and an antiperistaltic one on the right. He reported subsequent reflux on the right side, but it was noticeably absent on the left. In the present series an isoperistaltic anastomosis in unilateral, and a twisting loop in bilateral cases, presented no problems of blood supply or reflux.

The proximal ureteroileal anastomosis in our cases was of a direct type, as oblique tunnel anastomosis may lead to stenosis (Amin, 1976), and reflux is unlikely with this technique (Goodwin, 1960).

Goodwin (1960, 1974) found it most convenient to perform the distal anastomosis from inside the bladder. A circular window was excised from the posterior wall for an anastomosis; however, it is neither easy nor is it felt advisable to remove a disc of bilharzial wall if an adequate ileovesical anastomosis can be performed otherwise. No stenosis resulted in our 5 cases of direct anastomosis to the posterolateral opening.

It was found unnecessary to carry out proximal urinary diversion above the ureteroileal anastomosis, as advocated by Goodwin (1974).

Weinberg (1970) excised the diseased lower ureter but Amin (1976), although excising some segments, ignored others. In the presence of previous surgery or extravasation of urine, resection of the involved ureter can prove very hazardous, so simple ligation of the distal fibrosed ureter is recommended and in our cases presented no subsequent problem.

To guard against stasis in the loop it is important that any distal urinary obstruction should be dealt with before ileal loop replacement.

Cordonnier and Bowles (1970) explained the delayed dilatation of the ileal loop reported by Houtappel and Grundemann (1960) as due to distal urinary obstruction. However, Gibbon (1978; personal communication) noted the onset of dilatation of the loop, without evidence of distal obstruction, 15 years after ileocystoplasty for enuresis.

Tanagho (1975) dealt with 5 patients who had delayed decompensation of the bowel segment and is against incorporating intestinal loops into the closed urinary system.

McCullough *et al.* (1977), who used the ileum as a ureteric replacement in 12 patients, 7 of whom had solitary kidneys, found in a follow-up of 1 to 13 years that renal function was well preserved and electrolyte balance was minimal. Abrams and Buchbinder (1977) had a similar experience in 4 patients followed up for 4, 5, 11 and 12 years.

Fritzsche *et al.* (1975), in a radiographic review of 100 patients who had undergone ileal ureter operations between 1954 and 1975, found that vesicoileal reflux occurred consistently but without apparent harm. There was no decrease in parenchymal thickness or scarring, and dilatation of the pelvicaliceal systems was decreased or stable in the majority of cases.

Horiuchi and Hoshino (1975), in a study of 33 patients with loop reconstruction, found a tendency for hyperchloraemic acidosis and high blood urea to occur only in those patients with poor renal function. The degree and incidence of these changes was influenced by the length of ileal segment and the volume of urine excreted. Goodwin (1960, 1974) has repeatedly pointed out that the ileum should not be incorporated into the closed urinary system in patients with a pre-operative serum creatinine exceeding 0.2 to 0.25 mmol/l. An ileocutaneous diversion would be preferable.

Unfortunately, the patient with bilharzial disease is usually completely against any form of external diversion. An ileal ureter is thus the only alternative for such patients even in the presence of poor renal function. The loop should be as short as possible, and a high calorie, low protein diet with courses of sodium bicarbonate and urinary antiseptics post-operatively are advisable.

Regular follow-up to ensure proper emptying of the bladder and loop are essential.

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Pre-operative and Post-operative Evaluation of the Rectal Bladder

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Summary—Five Heitz-Boyer-Hovelacque operations in children were reviewed in which particular attention was paid to pre-operative examinations, including electromanometry (EMM) and post-operative evaluation of continence, functional result and renal function. In our limited experience the rectal bladder operation is a good procedure in selected cases; it produces satisfactory continence and maintains renal function.

In the rectal bladder operation, the ureters are implanted into the isolated rectum which functions as a continent urine receptacle. In the technique of Heitz-Boyer-Hovelacque, the colon is exteriorised at the anus through an intrasphincteric and retrorectal channél. In this way the anal canal is divided by a septum into 2 compartments, the anterior for urine and the posterior for faeces (Bracci, 1973).

This study gives our experience with this technique in 5 children.

Methods

The continent rectal bladder requires perfect voluntary and reflex control of the anal canal and sphincters. Therefore careful attention is paid to the following points in the pre-operative examination:

1. A history of both nocturnal and diurnal continence, especially during periods of diarrhoea. A minimum of co-operation and comprehension is necessary. Inspection of the anal canal must reveal no fissures, fistulae or prolapse (Strohmenger, 1973).
2. By recto-anal sphincteromanometry, the tone, motility, reflex activity and contraction force of the anal sphincter are measured. The normal pressure (Fig. 1) in the anal canal is about 30 to 50 mmHg; a fall in pressure is produced by insufflation of a balloon in the rectum; this reflex pressure fall is due to smooth muscle relaxation while the electromyographic activity in the external anal sphincter remains unchanged. On the contrary, an increase in pressure is noted during coughing or raised intra-abdominal pressure; this

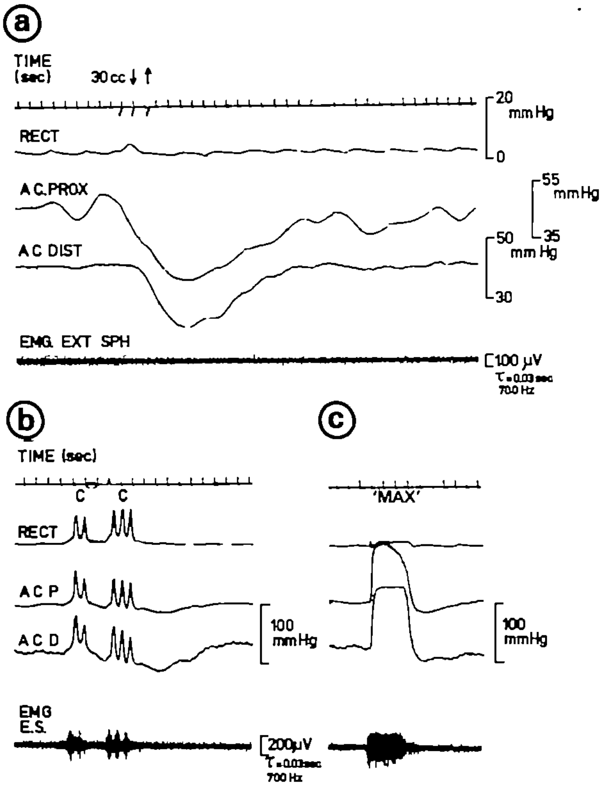

Fig. 1 Normal recto-anal sphincteromanometry. (a) normal recto-anal reflex at 30 ml ⁄ ⁄. (b) reflex contraction during cough (C). (c) maximal voluntary contraction. Rect: rectum; A.C.P.: anal canal, proximal part; A.C.D.: anal canal, distal part; E.M.G.-E.S.: electromyography in external anal sphincter.

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increase is due to a reflex contraction of the striated musculature of the anal sphincter. A maximal increase of anal pressure is noted during voluntary sphincter contraction (Kerremans, 1968).

3. Absence of denervation potentials in the anal sphincter is confirmed by electromyography in 4 quadrants of the sphincter (Kerremans, 1968).

It is evident that renal function must be evaluated pre-operatively by means of clearances and excretion urography. In addition, we perform a barium enema not so much to exclude pathology as to assess the length and distensibility of the colon.

Patients and Results

The most important data of the 5 cases are shown in the Table.

Case 1

S.R., a boy with bladder exstrophy. At the age of 3 years a Heitz-Boyer operation was performed. Post-operatively there were no complications. During the following 8 years continence improved progressively. The epispadias was corrected at the age of 12 years. Now, 13 years after the Heitz-Boyer intervention, diurnal continence is perfect but enuresis occurs twice

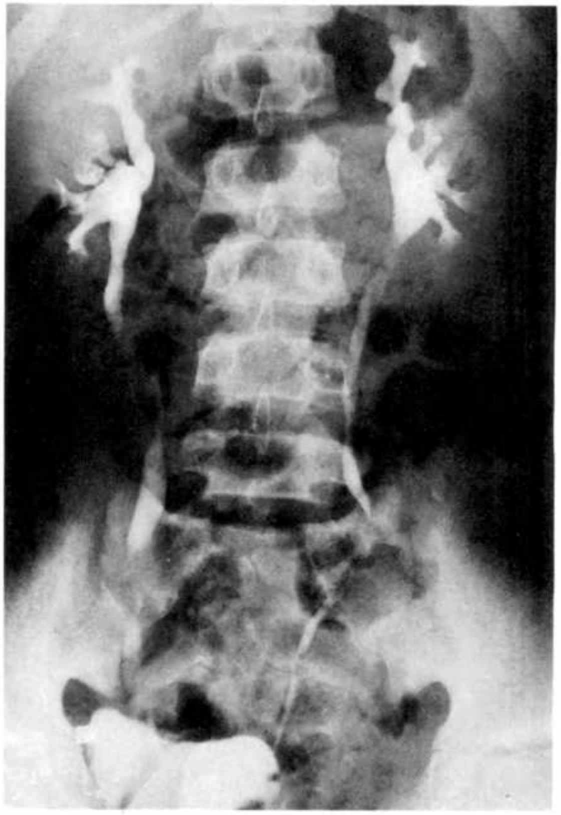

Fig. 2 Post-operative excretion urography.

Table

Case	*S.R. ♂*	*D.G. ♂*	*G.C. ♀*	*E.B. ♂*	*W.J. ♂*
Age at operation	*3 years*	*3 years*	*14 years*	*4 years*	*13 years*
Indication	*Bladder exstr.*	*Bladder exstr.*	*Bladder exstr.*	*Rhabdomyosarcoma*	*Neurogenic bladder*
Pre-operative anal EMM					
Basal tonus (mmHg)	—	48	68	60	60
First sensation of defaecation (ml)	—	15	20	5	20
Reflex contraction (mmHg)	—	—(40)*	104	88	—60*
Voluntary contraction (mmHg)	—	110	80	—	30?†
Age now	*15 years*	*6 years*	*15 years*	*5 years*	*16 years*
Post-operative anal EMM					
Basal tonus (mmHg)	68	40	40	48	68
First sensation of defaecation (ml)	40	15	20	25	20
Reflex contraction (mmHg)	52	80	60	80	80 (40)
Voluntary contraction (mmHg)	52	?	56	90	20?
Rectal bladder capacity (ml)	280	100	250	150	125
Continence					
Faeces	+	+	+	±	+
Urine day (n/d)‡	0	0-1	0	1-3	0
Urine night (n/n) §	1/3	1-2	0-1	incont.	0
Nocturia	1	0	1-2	0	1
Renal function	=	=	=	=	↘

* Only by perineal activation. † Poor co-operation. ‡ Napkins during the day. § Napkins at night.

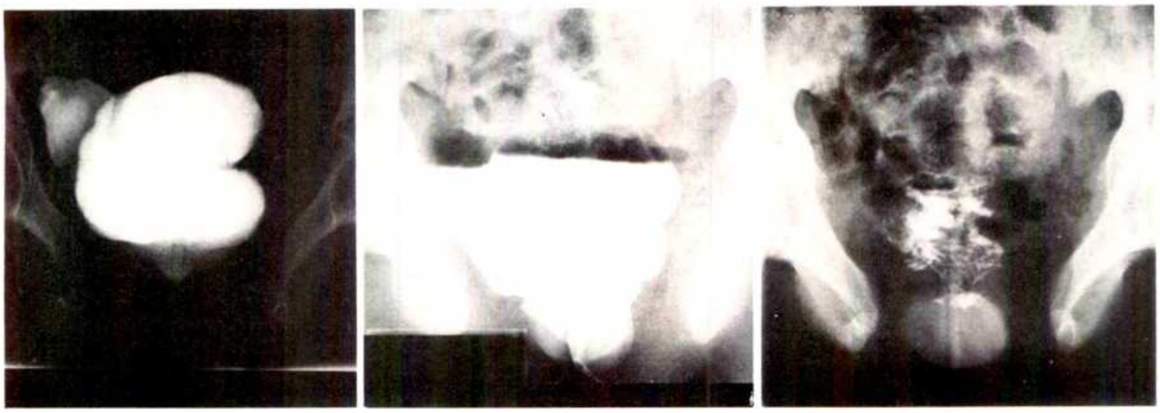

Fig. 3 Pre-, per- and post-micturition "cystography" of the rectal bladder.

weekly. The anal septum is clearly visible. The urine is mostly clear. Blood biochemistry is normal. The excretion urogram shows a normal upper urinary tract (Fig. 2). "Cystography" of the rectal bladder shows no reflux into the ureters or colon, a capacity of 280 ml, and no post-voiding residual urine (Fig. 3).

Case 2

D.G., a boy with exstrophic bladder and congenital inguinal hernia. A rectal bladder was formed at the age of 3 years. One year after the operation dilatation of the left ureter occurred because of stenosis at the implantation site, necessitating a reimplantation of the ureter. The boy is now 6 years old. He is free of infection, continent of urine and faeces during the day, but at night he continues to lose some urine and faeces. Blood urea, creatinine and electrolytes remain normal. The excretion urogram shows slight atony of the left ureter but the previous dilatation has completely regressed. On cystography a small rectal bladder of 100 ml capacity was noted, with reflux in to the sigmoid colon during voiding.

Case 3

G.C. This girl had a primary closure of an exstrophic bladder at the age of 3 months. Following the operation she had total incontinence with a bladder capacity of only 75 ml. At the age of 14 years a Heitz-Boyer procedure was performed. The first pyelogram 2 weeks post-operatively showed bilateral dilatation of the ureters

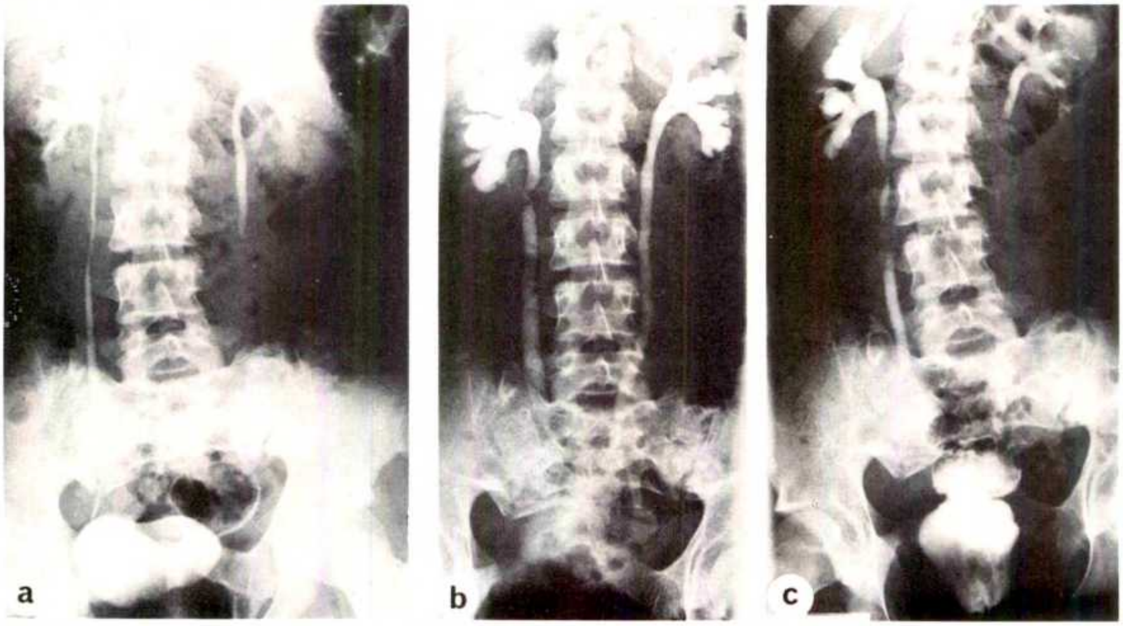

Fig. 4 (a) Pre-operative excretion urography; (b) 14 days post-operative: bilateral dilatation of ureters and pelves; (c) 3 months post-operative: regression of dilatation.

and pelves; however, a repeat pyelogram 3 months after the operation showed complete regression of the dilatation on the left side and almost complete regression on the right (Figs. 4a, b, c). Three months after the operation the girl states that she is perfectly continent during the day and night but she goes to the toilet once or twice at night. She has good differential sensation between urine and faeces. On cystography a rectal bladder capacity of 250 ml was noted, with only slight overflow into the sigmoid during micturition. Figure 5 shows the pressure in the proximal and distal anal canal and reflex pressure fall in the anal canal after insufflation of a balloon in either the rectal bladder (Fig. 5a) or the sigmoid colon (Fig. 5b). The basal pressure is slightly reduced in comparison to the pre-operative values, but both compartments have the same inhibitory reflex effect on the anal canal.

Case 4

E.B. At the age of 1 year and 3 months this boy underwent a total cystoprostatectomy for rhabdomyosarcoma of the urogenital sinus. A double ureterostomy was made in the middle of the abdomen. Three years after the procedure and subsequent irradiation and chemotherapy, there was no evidence of local tumour recurrence or generalised metastases. At the parents' request the external urinary diversion was converted into a rectal bladder. Biochemical studies and excretion urography show no change since the intervention 6 months ago; however, the child is incontinent at night and soils 1 to 3 napkins during the day. The septum is clearly visible at the anus. Electromanometry of the anal canal shows normal values.

Case 5

W.J. This boy with a spastic neurogenic bladder had several congenital malformations including a fusion abnormality of the cervical spine, club feet, bilateral cryptorchidism and psychological and motor retardation. Because of progressive deterioration of renal function with bilateral hydronephrosis, pronounced vesicoureteric reflux and a large volume of residual urine, a cystostomy was performed. Two years later his parents requested closure of the cystostomy. We tried external urethral sphincterotomy and bladder re-education without success; the residual urine remained infected and of large volume. Since a permanent external diversion was refused, we decided to perform a Heitz-Boyer operation. The clinical result is perfect. The patient is continent of urine and faeces. However, renal function shows a slow but progressive deterioration. Since excretion urography and rectal bladder cystography show no sign of post-operative complications, we presume that the deterioration is mainly due to progression of the severe pyelonephritic lesions already present before the intervention. Because of mild acidosis, therapy with bicarbonate has been started. The rectal bladder has a capacity of at least 125 ml on rapid filling. During

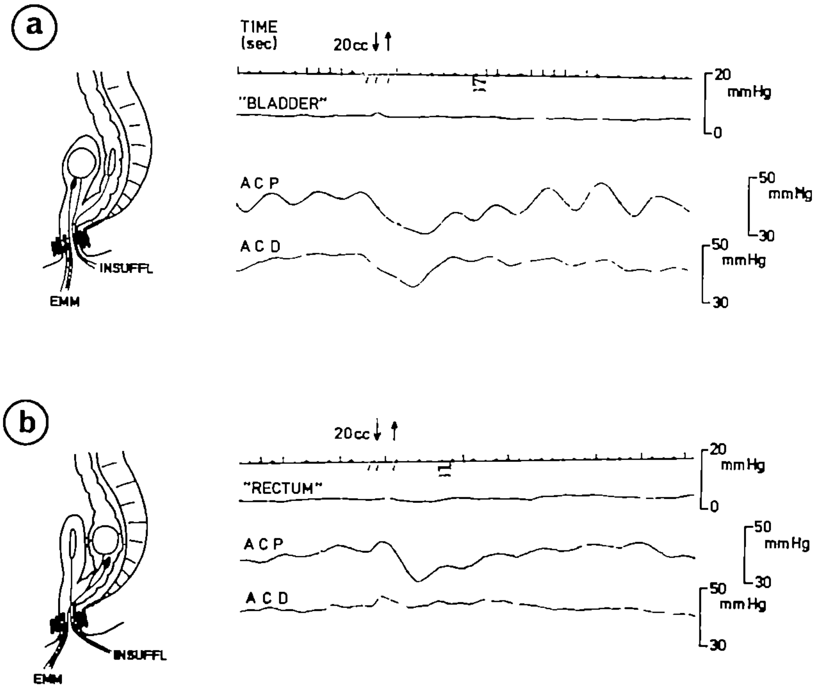

Fig. 5 Post-operative recto-anal sphincteromanometry. (a) Normal recto-anal reflex after distension of the rectal bladder (at 20 ml / /). (b) Normal recto-anal reflex after distension of the sigmoid colon (at 20 ml / /).

voiding a slight overflow is noted into the most distal part of the sigmoid colon.

Discussion

The main indications for rectal bladder diversion are bladder exstrophy and following cystectomy. We believe that a neurogenic bladder is not an indication, although we obtained one good result. The main question is whether the rectal bladder fulfils its double aim, which is to produce continence and to maintain normal renal function.

Functional Result and Continence

Older children have a better functional result than younger ones, regardless of age at the time of operation. Cases 1 and 3 became continent at the age of 15 years although the former was operated on at the age of 3 years and the latter only 5 months ago. Thus age seems to be more decisive than the length of the post-operative period. This confirms the experience of Duhamel (1971) and Bottou and Bakali (1978). It is therefore necessary to decide the optimal age for the intervention by consulting with the parents.

Continent patients empty the bladder at least once at night. This habit should be taught to younger children.

There is poor correlation between continence and the values of the post-operative manometry. Subnormal post-operative values (case 3) can be associated with satisfactory functional results, whereas normal values do not necessarily guarantee continence (case 2). However, we are convinced that pre-operative manometry and electromyography should be normal because post-operative diminution of these values may occur. In particular, the force of the voluntary anal contraction seems to diminish. Therefore we think that better and earlier continence could be achieved by intense post-operative training of the anal sphincter, if necessary by electronic stimulation.

Maintenance of Renal Function

In the absence of hydroureteronephrosis caused by post-operative obstruction, renal function remains normal or at least unchanged as compared to the pre-operative values. We have already discussed the possible causes of the mild renal deterioration observed in case 5.

Since no electrolytic disturbances occur, daily medication is unnecessary. This is a significant advantage in comparison to ureterosigmoidostomy, which frequently causes hyperchloraemic acidosis and hypokalaemia (Bettex *et al.*, 1971). Absence of ionic disturbances can be explained by the fact that absorption from the rectum is less than from more proximal segments of the colon, into which only slight reflux sometimes occurs during micturition.

None of our patients has had an attack of acute pyelonephritis and none has formed stones.

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Supersensitivity to Prostaglandin in Chronic Neurogenic Bladders

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Summary—The bladder response to prostaglandin (PG test) was investigated in chronic neurogenic bladders by isometric cystometry and compared with the results obtained from normal subjects. The urinary bladder was filled with 100 ml of saline and 100 μg of prostaglandin 995 were injected intravenously. The changes in bladder and intra-abdominal pressures were observed for up to 20 min. A rise in detrusor pressure of more than 20 cm of water was judged a positive response. Out of 21 neurogenic bladders 12 had a positive response. The result of the PG test demonstrated a good correlation with the supersensitivity test to bethanechol chloride which was performed on these patients on a different day. All of the normal subjects had negative responses. It was concluded that the chronically denervated bladder is supersensitive to prostaglandin 995.

Prostaglandins were first isolated by von Euler in 1936 from the prostate and seminal vesicles of mammals. The recent *in vitro* experiments (Taira, 1974; Abrams and Feneley, 1976; Bultitude *et al.*, 1976; Andersson and Persson, 1977) have demonstrated that the E and F series of prostaglandins increase the tonus of detrusor muscle. This response has been inhibited by indomethacin and isoprenaline but not by tetrodotoxin, phenoxybenzamine, atropine or physostigmine.

In 1962 Lapides *et al.* introduced a test to identify the chronically denervated bladder by subcutaneous injection of bethanechol chloride. This test was modified by Glahn in 1970 (Lapides-Glahn test). The test is based upon the law of denervation (Cannon, 1939), *i.e.* once the organ is deprived of its efferent neurons it demonstrates an increased irritability to chemical agents after a certain period of time. During the course of clinical studies on prostaglandin we noticed an elevation of bladder tonus in several of our neurogenic bladder patients. The aim of this study is to find out whether the chronically denervated bladder exhibits a supersensitivity to prostaglandins.

Patients and Methods

The neurogenic bladder group consisted of 16 male and 5 female patients whose ages varied from 6 to 78 years (mean 44±22). Of these patients 16 had bladder dysfunction secondary to spinal cord lesions, 3 due to detrusor hyperreflexia, 1 due to tabes dorsalis and 1 to the Shy-Drager syndrome. The duration of bladder dysfunction varied from 4 months to 32 years. Supranuclear lesions were found in 9 and nuclear or infranuclear lesions in 12. Cystometric assessment of the bladder revealed a reflex bladder in 4 patients, uninhibited in 2 and autonomous in 15.

The control subjects were made up of 9 males and 1 female aged from 13 to 78 years (37±20) who had neither functional nor organic disorders in their lower urinary tract.

The purpose of this investigation was fully explained to both the patients and controls. Patients who were pregnant or who had severe cardiovascular disease were excluded.

Cystometry

Conventional slow-filling cystometry was performed with 2 rubber catheters of 10 FG and 12 FG in the urethra; saline was infused at 70 ml per min through one catheter and the other was used to record bladder pressure via a strain gauge transducer. Intra-abdominal pressure was recorded using a rectal balloon. It was essential to monitor the detrusor presssure, *i.e.* the bladder pressure minus intra-abdominal pressure, as this was the pressure change by which the test was being

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Table Correlation of PG test and Lapides-Glahn test in 21 neurogenic bladder patients

		PG test		
		+	±	−
	+	11	1	0
Lapides-Glahn test	±	1	1	1
	−	0	1	5

evaluated. These changes were registered on a 2-channel electric recorder (RM-20, Nihon-Koden).

Lapides-Glahn Test

The bladder was filled with 100 ml of saline and a 10 FG catheter left in the bladder to record the pressure. After stabilisation of the pressure the supersensitivity to bethanechol was tested using the technique described by Glahn (Glahn, 1970); 2.5 mg bethanechol chloride (Besacolin, Eisai Pharmaceutical Ltd) were subcutaneously injected into the normal tissues of the thigh, followed by massage. The changes in bladder tonus and intra-abdominal pressures were recorded for a period of 30 min unless a significant rise in detrusor pressure had occurred before that time. In the case of children the dose was reduced to 1.5 to 2.0 mg. Because of their reaction to bethanechol 3 patients required atropine. Evaluation of the results was based upon the modified criteria used by Glahn (1970). If the detrusor pressure rose by more than 20 cm of water the test was deemed positive. If the pressure rose by 15 to 20 cm of water the test was inconclusive and if the pressure rose by less than 15 cm of water the test was negative. The control subjects did not undergo this test.

PG Test

The supersensitivity of the bladder to prostaglandin was tested on a separate day but within 2 weeks of the bethanechol test. The procedure and evaluation of the test were similar to the Lapides-Glahn test. With the bladder filled to 100 ml and the pressure stabilised, the patients were given 100 μg of PG 995 intravenously over a 30-s period. Three patients and 6 controls had 150 to 500 μg (mean 302 μg) in a 4- to 9-min intravenous injection (0.5 to 2.5 μg/kg/min) in an attempt to find the optimal dose response. PG 995 (16-(3-trifluoromethylphenoxy)-ω-tetranor-trans-Δ^2-$PGF_2\alpha$ methyl ester) is a derivative of $PGF_2\alpha$ (ONO-995, Ono Pharmaceutical Ltd). The change in bladder and intra-abdominal pressures was monitored for a 20-min period or until a significant change was observed.

Results

Of the 21 patients with neurogenic bladders 12 showed a positive response, 3 inconclusive and 6 negative. The overall result of the PG test showed a good correlation with that of the Lapides-Glahn test (Table). Figures 1 to 3 show, schematically,

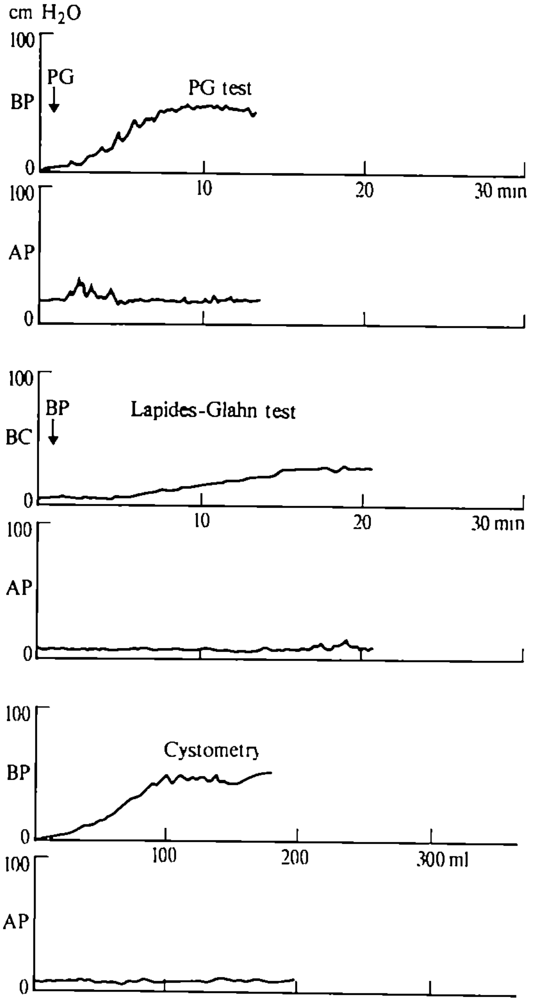

Fig. 1 M.S., 62-year-old male: 12 months after spinal fracture at C6 followed by laminectomy. PG test and Lapides-Glahn test show a positive response. Autonomous bladder is shown at the bottom. PG, intravenous injection of PG 995 100 μg. BC, subcutaneous injection of bethanechol chloride 2.5 mg. BP, bladder pressure. AP, intra-abdominal pressure.

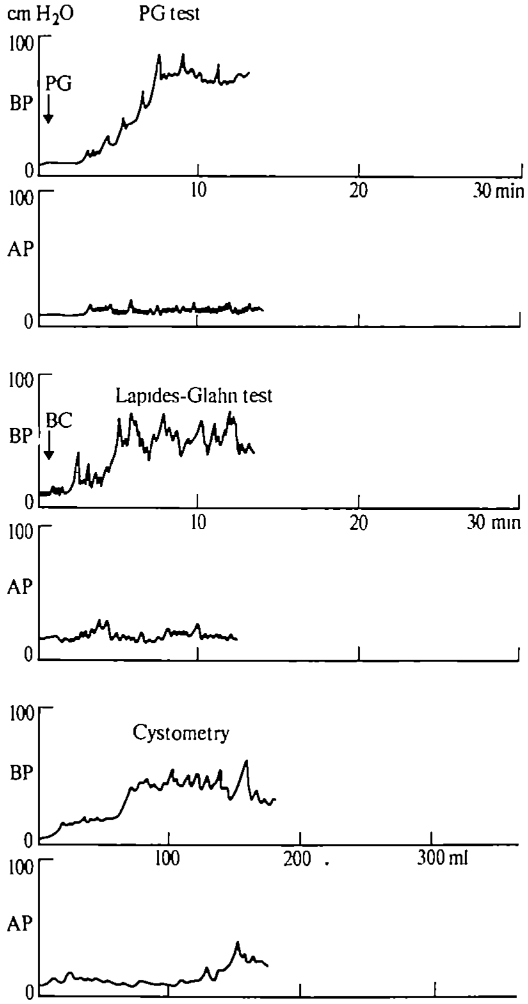

Fig. 2 R.N., 8-year-old female: 2 months after laminectomy at L4 due to lipomyelomeningocele and tethered cord syndrome. The sharp rise in bladder pressure reflects the change in intra-abdominal pressure. PG test and Lapides-Glahn test demonstrate a positive response. Autonomous bladder is revealed by the cystometry. PG, prostaglandin 995 100 μg i.v. BC, bethanechol chloride 2.5 mg s.c. BP, bladder pressure. AP, intra-abdominal pressure.

the typical recordings of the PG test in comparison with the Lapides-Glahn test and cystometry. None of the control subjects showed a positive supersensitivity to PG 995, their pressure rises being less than 7.5 cm of water.

Discussion

Prostaglandin is known to be distributed in almost every organ of the body. In obstetrics, prostaglandin has been widely used to facilitate normal delivery. Bultitude *et al.* (1976) reported that 14 out of 21 female patients with difficulty in urination had been successfully treated by the instillation of 500 μg of PGE_2 into the bladder. On the other hand, *in vitro* experiments have suggested that prostaglandin might play a role in maintaining bladder tonus rather than facilitating micturition. This has been shown by the slow contraction and relaxation of the detrusor in response to prostaglandin, a response which differs from that recorded from acetylcholine activity. The mechanism of prostaglandin action on the detrusor is thought to be either a direct action upon the muscle (Taira, 1974; Andersson and

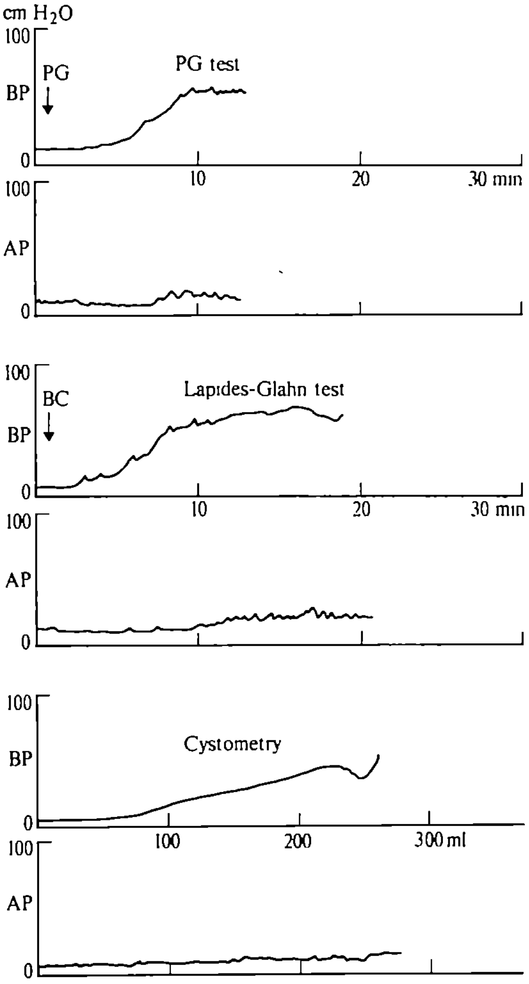

Fig. 3 K.A., 58-year-old female. Tabes dorsalis for 32 years. A positive supersensitivity to PG 995 100 μg (PG) and bethanechol chloride 2.5 mg (BC). Cystometry revealed an autonomous bladder. BP, bladder pressure. AP, intra-abdominal pressure.

Persson, 1977) or a modulating effect upon normal nervous transmission (Choo and Mitchelson, 1977). The bethanechol test depends upon the supersensitivity of the chronically denervated bladder to parasympathomimetic drugs. The present study has shown that the denervated bladder also responds to PG 995 with a similar supersensitivity. This is not surprising, since both bethanechol and prostaglandin mimic the role of a natural chemical mediator, acetylcholine, by contracting the detrusor muscle. Several factors are responsible for the development of this supersensitivity, *e.g.* the increase in size of receptor area to acetylcholine (Axelsson and Thesleff, 1959), removal of neural influence (Miledi, 1960), diminished enzyme activity and change in permeability (Goth, 1968).

PG 995 did not significantly change the bladder tonus in the control subjects, but caused urgency of micturition in 8 and a sensation of abdominal fullness with little increase in bowel peristalsis in 7. When PG 995 was given to patients with chronic neurogenic bladders, a slow and sustained pressure rise was seen, starting 3 to 5 min after injection and rising to a maximum response in 8 to 12 min. Autonomous contraction waves and sharp pressure rises reflecting intra-abdominal pressure changes were often superimposed upon the detrusor response to the prostaglandin (Figs. 1 and 2). Voiding was not encountered in any of the patients in the present series; however, intermittent leakage of urine around the catheter was noted in 2 patients who had been previously subjected to sphincterotomy. Several patients, in contrast to the control subjects, demonstrated vigorous contraction of the intestine which facilitated bowel movement during or after the test. The intravenous injection of PG 995 100 μg (approximately 2 μg/kg) was well tolerated by the majority of cases. Four patients complained of nausea during the test and one vomited later. It is interesting to note that the response to PG 995 was more pronounced than that to bethanechol in respect of both intensity and time. A higher elevation of bladder tonus was observed 5 to 10 min earlier than with bethanechol. The difference in route of drug administration is responsible for this time factor, which saves time and also avoids any possible artefact from urine accumulation during the test (Glahn, 1970). PG 995 is contraindicated in pregnant women because of its abortifacient effect.

Seventeen patients showed the same response to PG 995 and bethanechol: positive 11, inconclusive 1 and negative 5. In 4 patients the results varied, although the pressure differed by only a few cm of water in each case. The negative response is probably due to incomplete denervation and/or regeneration of nerve fibres. The modified criteria for the evaluation of the results for the bethanechol test (Glahn, 1970) were also valid for the PG test.

It is concluded that the chronically denervated bladder is supersensitive to prostaglandin and that the PG test could be considered as an alternative to the Lapides-Glahn test.

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Experimental Trypsin-induced Urothelial Cell Separation *in vivo*

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Summary—A morphological study of the effects of different concentrations of trypsin on the normal rat bladder *in vivo* is described. A low concentration (5000 u/ml) of the pure enzyme caused extensive urothelial cell separation following intravesical instillation via a catheter for 30 min. Urothelial regeneration commenced within 12 h and the appearance of the bladder was normal within 3 months. However, the development of submucosal haemorrhage and ulceration, partly as a result of infection, indicates that further experimental work is required before trypsin can be evaluated clinically for removing *in situ* carcinoma or reducing tumour bulk. The enzyme might also be used to produce more cellular material for cytological examination.

The proteolytic enzyme trypsin can be used to separate bladder epithelium for *in vitro* studies (Bonar *et al.*, 1977). Should trypsin have a similar action *in vivo*, then it might be possible selectively to remove malignant cells. Thus the enzyme could have a therapeutic role by removing widespread flat *in situ* carcinoma (CIS) or by reducing tumour bulk. In order to assess the possible clinical value a morphological study has been made of the effect of trypsin at different concentrations on rat bladder urothelium *in vivo*.

Materials and Methods

The experiments were performed on female Sprague-Dawley rats aged between 2 and 4 months and weighing 180 to 320 g. Anaesthesia was produced by an intraperitoneal injection of diazepam (Valium, Roche) 2.5 mg/kg, followed by an intramuscular injection of neuroleptanalgesia (Hypnorm, Janssen) 0.5 mg/kg. To minimise infection, each animal was given a subcutaneous injection of 1 ml of a saturated solution of chloramphenicol (Parke-Davis) and the perineal region was swabbed with alcoholic hibitane immediately before catheterisation: 30 cm nylon intravenous catheters (Luer 2 FG, 200/300/010, Portex Ltd) were used. At the conclusion of each experiment the bladders were bisected and routinely processed for histology using haematoxylin and eosin stains. In selected cases, Van Gieson's stain for collagen, Perls' stain for iron, Von Kossa's stain for calcium, Martius' scarlet-blue stain (MSB) for fibrin and Gram's stain for organisms were used.

Trypsin was obtained in a "highly purified" crystalline state (Tryptar, Armour Pharmaceutical Co) in vials each containing 250,000 US National Formulary Units. This material is derived from mammalian pancreas glands and contains the enzymes trypsin and chymotrypsin.

Short-term Effects of Trypsin

Twenty rats were each given an intravesical injection of 2 ml trypsin in sterile water at concentrations of 12,500 u/ml or 5000 u/ml. After 30 min the contents were aspirated and the bladders were washed with 3 aliquots of 2 ml each of sterile water, aspirating the fluid between washes. Two animals were killed immediately, then 2 each at hourly intervals up to 6 h and at 12, 18 and 24 h.

Long-term Effects of Trypsin

Four groups of 26 animals were given an intravesical injection of trypsin at concentrations of 5000, 12,500 or 25,000 u/ml or sterile water (2 ml/injection). After 30 min the contents of each bladder were aspirated and the bladders washed with sterile water as already described.

From each of these 4 groups, 2 animals were killed immediately, then 2 at daily intervals up to 1 week and at 2 weeks. It was planned to kill a further 4 animals from each group at 4 weeks,

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Table Summary of the Morphology Changes Observed During the 3 Months Following Intravesical Treatment or Rat Bladders with 5000 u/ml of Trypsin

Time after treatment	*Morphological changes observed after 30 min treatment with 5000 u/ml of trypsin*
0 hours	1. Urothelial shedding seen. 2. Some basal cells partly adherent to basement membrane and projecting into the lumen, although detached from adjacent mucosal cells. 3. Elsewhere, strips of urothelium partly detached from basement membrane (Fig. 2).
1 to 2 hours	1. Urothelial shedding more extensive; also ballooning, with vacuolation of nuclei and cytoplasm, in adherent and detached cells. 2. Congestion of submucosal vessels with thrombi in some lumina. 3. Neutrophils adherent to vascular endothelium. 4. Small submucosal haemorrhages.
3 to 12 hours	1. The changes described above more pronounced, with more acute inflammatory changes, vessel congestion and extensive submucosal haemorrhage: continuing urothelial degeneration (Fig. 3). 2. Generalised submucosal oedema. 3. Small haemorrhagic foci in bladder muscle. 4. Endothelium of many submucosal vessels damaged; exudate sometimes extending into the submucosa (Fig. 4).
12 to 18 hours	1. Elongated cells with large nuclei and basophilic cytoplasm stretched over the denuded surface. Subsequently these cells became more cuboidal. 2. Some mitoses seen in this layer (Fig. 5). 3. Acute inflammatory changes still present, but now more focal.
18 to 24 hours	1. Most of bladder covered by a layer 2 to 3 cells thick: mitoses more numerous. 2. Submucosal oedema less marked. 3. Acute inflammation limited to small ulcerated areas. 4. Little evidence of residual muscle damage.
48 hours	1. Further urothelial regeneration seen. 2. Submucosa still oedematous, but less fibrinous exudate. 3. Circumscribed ulcers persisted.
3 to 7 days	1. Urothelium now 5 to 6 layers thick in most areas (Fig. 6). Some squamous metaplasia. 2. Colonies of organisms identified at ulcer sites in 8/10 specimens. 3. Ulcers persisted, their bases extended into muscle (Fig. 7).
14 days	1. Normal mucosa in one specimen and squamous metaplasia surrounding an infected focus in the other. 2. Disappearance of submucosal oedema.
1 month	1. Complete lining of squamous epithelium 5 to 6 cells thick in all 4 specimens. 2. No infection observed. 3. Submucosa normal except for occasional macrophages containing iron pigment and increased numbers of mononuclear cells, probably histiocytes. 4. Most of muscle coat normal, apart from scattered foci of granulation tissue with some fibroblasts between muscle bundles. These changes were occasionally seen on the serosal surface.
3 months	1. Urothelium, 3 to 4 cells thick, seen in 4 specimens. In the fifth specimen, which contained a stone, there was papillomatosis with keratinising squamous metaplasia (Fig. 8) and diffuse chronic inflammation in the adjacent stroma. 2. No evidence of infection. 3. Small epithelial "rests" present in the stroma in some areas. 4. Submucosa normal except for increased numbers of stroma cells. No fibrosis. 5. Muscle layer normal except for occasional foci of iron-containing macrophages and calcification.

and 6 at 12 weeks. However, some animals died during the course of the experiment, so that the numbers of animals killed at 4 and 12 weeks respectively were: 3 and 5 controls; 4 and 5 at 5000 u/ml; 2 and 5 at 12,500 u/ml; 3 and 4 at 25,000 u/ml.

Results

Short-term Effects of Trypsin

Control rat bladders were lined by urothelium in which 3 layers of cells were present (Fig. 1). The morphological changes observed in the rat bladder

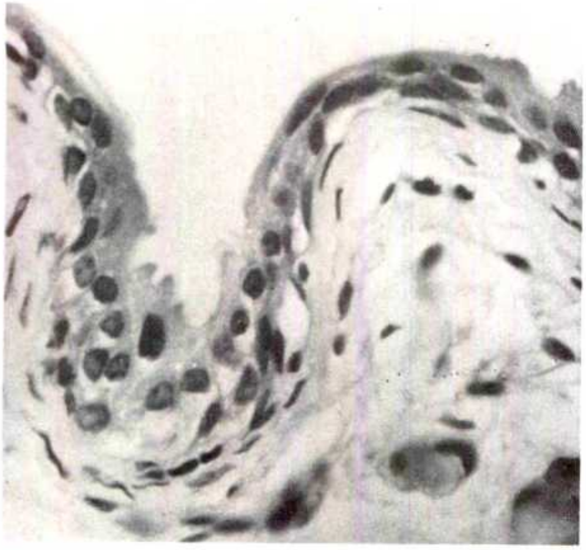

Fig. 1 Control. Normal rat bladder urothelium, 2-3 cells thick (H and E ×640).

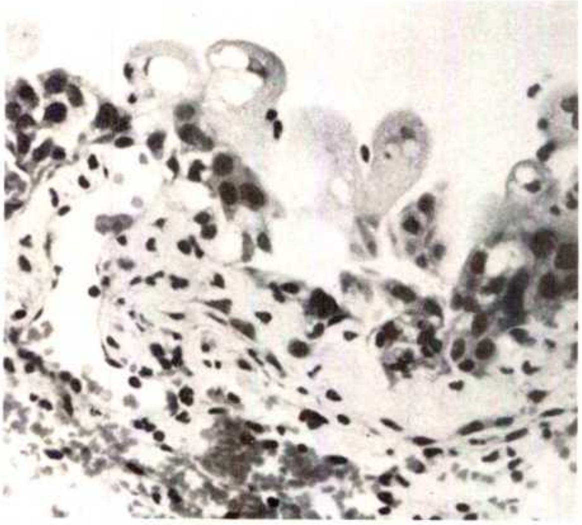

Fig. 3 Trypsin 5000 u/ml. 3h. Cytoplasmic ballooning and vacuolation of partly detached urothelial cells. Submucosal haemorrhage (H and E ×400).

following a 30-min treatment with 5000 units/ml of trypsin are detailed in the Table. In summary, extensive denudation of the urothelial surface was followed by limited submucosal damage with ulceration. Urothelial regeneration started within 12 h and mitoses were numerous by 24 h, at which time there was little evidence of muscle damage.

In general, the effects produced by the higher concentration (12,500 u/ml) were similar but more pronounced. For example, by 1 h the urothelial shedding was more extensive, so that denudation was virtually complete. At 3 h the vascular damage was much more severe. There were more thrombi in vessels and a greater acute inflammatory response. Foci of haemorrhage disrupted muscle bundles and occasionally extended into the serosal fat. At 24 h these changes persisted and the inflammation and haemorrhage beneath the ulcers extended through the thickness

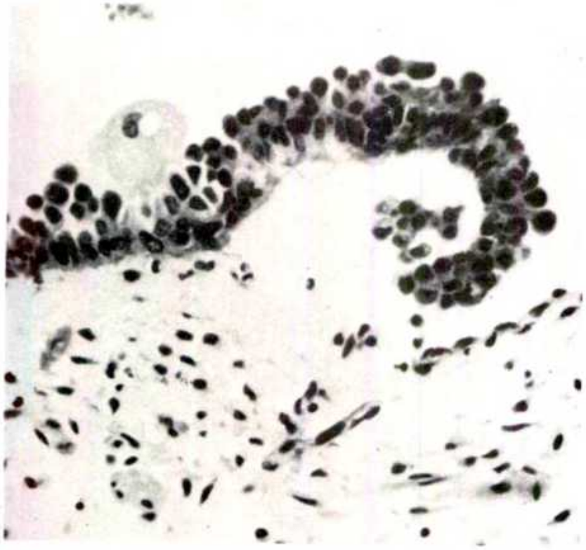

Fig. 2 Immediately following 30 min treatment with purified trypsin, 5000 u/ml. Partial stripping of urothelium. Early detachment of individual cells (H and E ×160).

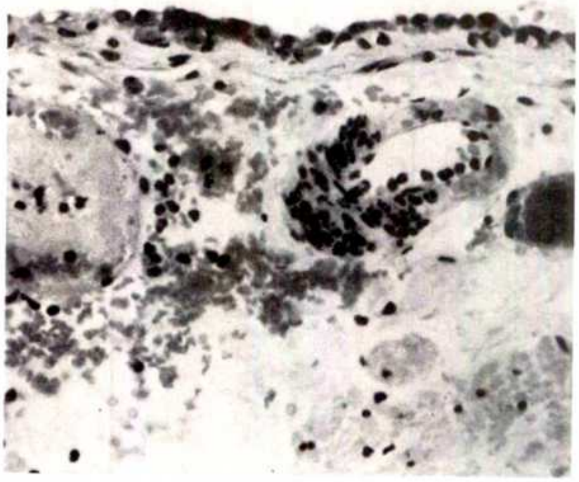

Fig. 4 Trypsin 5000 u/ml. 6 h. Single layer of urothelial cells which remain partly attached. Oedema of submucosa, with haemorrhage, and neutrophil leucocytes around vessel wall (H and E ×160).

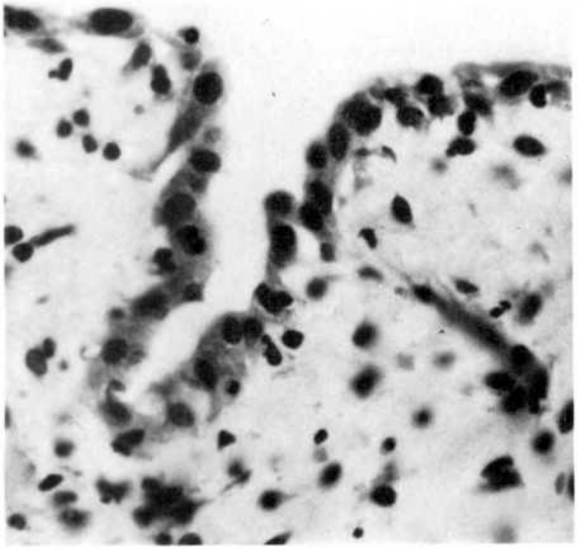

Fig. 5 Trypsin 5000 u/ml. 12 h. Early regeneration. Single layer of elongated, basophilic cells over surface. One mitosis (H and E ×640).

of the whole wall, which appeared thinner than normal.

In all specimens examined the epithelium of the ureters was not affected.

Long-term Effects of Trypsin

The morphological changes seen in the 3 months following treatment with 5000 u/ml of trypsin are given in the Table. Urothelial regeneration continued, producing a 5-6 cell thick layer within 3 days and persisting at 1 month after treatment, but returning to the normal 3-4 cell thick layer by 3 months. Infection was noted after 3 days but had disappeared in specimens examined at 1 month.

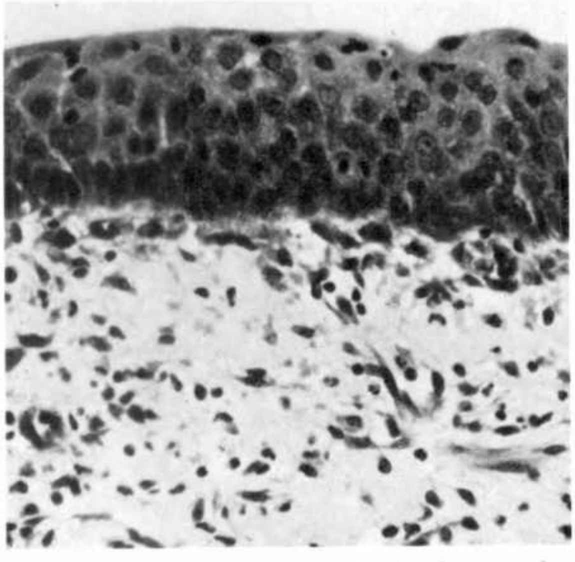

Fig. 6 Trypsin 5000 u/ml. 5 days. Continued regeneration: urothelium 6 cell layers thick, with squamous metaplasia (H and E ×400).

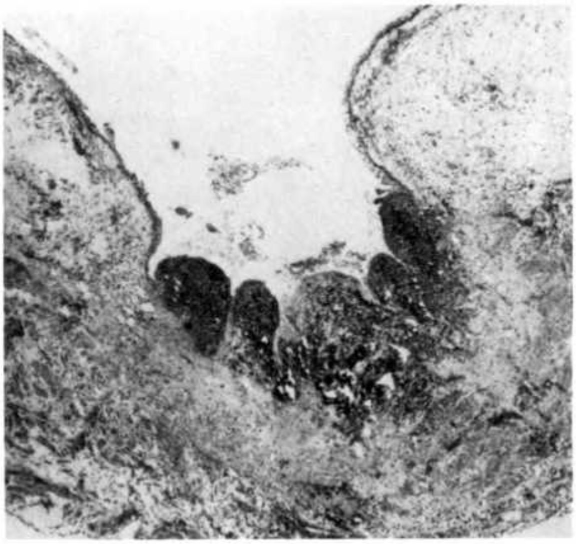

Fig. 7 Trypsin 5000 u/ml. 5 days. Infected bladder. Ulcer has penetrated muscle of wall. Regenerating urothelium adjacent (H and E ×80).

The changes observed following treatment with the higher concentrations of trypsin (12,500 and 25,000 u/ml) were similar but more pronounced. For example, most complete urothelial shedding occurred following exposure to the highest concentration, but with extensive ulceration and haemorrhage and damage of up to 50% of the wall at 24 h. By 48 h, haemorrhage and necrosis were observed which extended through the muscle wall, and by the third day both of the 25,000 specimens were infected and most of the bladder walls were involved with necrosis and infection. Gram-staining of the infected specimens showed colonies of Gram-positive cocci and numerous Gram-negative rods.

During the succeeding month the ulcers began to resolve, associated in some specimens with squamous metaplasia, calcification within the lumen (surrounded by papillary folds) and in the wall, and early submucosal fibrosis. By 3 months most of the highest concentration specimens showed squamous metaplasia with, in one case, keratinisation. In addition submucosal and, in one specimen, interstitial fibrosis was also

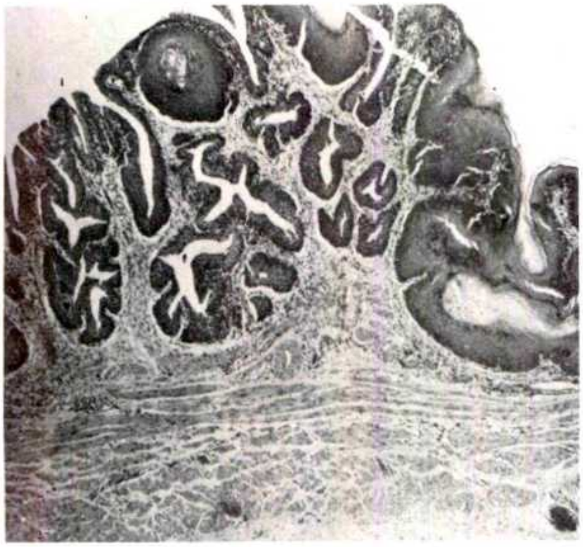

Fig. 8 Trypsin 5000 u/ml. 3 months. From bladder with stone. Papillary hyperplasia and keratinising squamous metaplasia of urothelium. Muscle layer is intact (H and E × 80).

observed. Papillomatosis was present in association with stones in 3 bladders at 3 months, one from each concentration group. One was analysed and found to consist of 90% magnesium-ammonium-phosphate and the remainder calcium phosphate.

Discussion

The experiments were designed to investigate the morphological changes in the bladder following treatment with trypsin over the concentration range 5000 to 25,000 u/ml. Extensive urothelial shedding, either of individual cells or of the whole surface layer, was observed during the 12 h following treatment. Consideration of the many other factors (apart from concentration) which affect the action of trypsin (Waymouth, 1974) is reserved for future studies.

Preliminary experiments not reported here had shown that crude trypsin (Difco 1:250) at concentrations of 0.1 to 10% could cause more extensive damage than the purified preparation. In addition, concentrations of the purified enzyme in excess of 25,000 u/ml were associated with a significant mortality.

In addition to removing the urothelium, trypsin appeared to enter the submucosa and cause oedema and even haemorrhage. The early appearance of acute inflammatory cells first around vessels and then ulcers is also probably related to the action of trypsin, as infection was not observed until a later stage. The highest concentrations of trypsin caused the greatest amount of damage and were associated with a 100% incidence of widespread infection. There was no evidence that catheterisation alone increased susceptibility, since none of the controls had histological evidence of infection.

There was very little evidence that trypsin caused direct damage to the muscle wall at the concentrations used in this study. However, once infection was established it usually spread into the deeper layers with full thickness involvement in some of the highest concentration specimens. The presence of iron within macrophages between muscle bundles in an otherwise normal bladder in the long-term experiments suggests that some enzyme had penetrated the full thickness of the wall, causing vessel wall damage and haemorrhage. However, there did not appear to be any associated fibrosis in the 5000 u/ml specimens.

The presence of stones is of interest. These were probably formed by calcification of necrotic tissue shed into the bladder lumen. The biochemical composition of these stones, principally magnesium-ammonium-phosphate, is consistent with an infective origin.

Despite evidence of extensive mucosal and submucosal damage, regeneration of the epithelium commenced rapidly. Basophilic, elongated cells with occasional mitoses extensively covered the surface at 12 h. By 18 to 24 h abundant mitoses and the appearance of a multi-cell layer confirmed that regeneration was occurring. Squamous metaplasia was most pronounced immediately adjacent to persisting infected and ulcerated areas in earlier specimens, and was most marked in later specimens in association with stones, suggesting that it was related to infection and chronic irritation.

The rapid regeneration and hyperplasia resulting in a multilayered epithelium with submucosal invaginations and papillary hyperplasia appear to be a direct result of the trypsin-induced damage, since it was seen in both non-infected and infected bladders. Similar changes have been reported in the rat bladder after intraperitoneal cyclophosphamide (Koss, 1967) and in response to non-specific injury, for example topical application of a frozen rod (Shirai *et al.*, 1978). There is no definitive evidence that the papillary change in the rat bladder corresponds to the papillary neoplasm in the human, as it may represent florid hyperplasia, induced in this model by continued irritation by calcified debris or stones. The presence of this material appears to be related to keratinizing squamous metaplasia, which was only seen in association with stones.

The major purpose of this study was to determine whether trypsin might be useful therapeutically in removing carcinoma *in situ*, reducing tumour bulk, and possibly by increasing the material available for cytological examination. It was shown that trypsin is highly effective in separating urothelial cells, but it has not yet been determined whether trypsin is clinically applicable. While deleterious effects were observed, the lowest concentration (5000 u/ml) caused minimal damage whilst extensively removing urothelium. Before trypsin is evaluated clinically, infection must be prevented and it has to be confirmed in longer term (12 months or more) experiments that the papillomatosis, if it occurs in the absence of infection, is not a pre-malignant lesion. Comparing this treatment with those currently used for bladder cancer, such as cyclophosphamide, the effects of the low doses of trypsin do not appear to show any greater damaging side effects. It is considered that further experimental studies, particularly using lower concentrations of trypsin, might evaluate whether the enzyme has a useful clinical role.

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Pituitary Ablation in the Relief of Pain in Advanced Prostatic Carcinoma

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Summary—Fifty-five patients with diffuse pain due to bone metastases from prostate carcinoma were treated by pituitary ablation (53 with intrasellar Yttrium^{90} and 2 with intrapituitary alcohol instillation). The provisional criteria of the British Prostate Group were used to assess results. Post-operatively, 44 patients (80%) were significantly free of pain and 12 of them were completely pain-free. In only 11 cases (20%) was there no relief of pain. Of the 39 patients who required narcotics before ablation, only 12 required them post-operatively. Pituitary ablation with Yttrium^{90} has an important place in the relief of pain in advanced carcinoma of the prostate, although survival is not increased.

In many patients with advanced carcinoma of the prostate, widespread metastatic pain becomes the major clinical problem; being diffuse rather than localised, it is extremely difficult to treat and generally requires large quantities of narcotics. In previous reports from this Institute, Fergusson and Phillips (1962) and Fergusson and Hendry (1971) showed that pituitary ablation with radioactive Yttrium brought considerable pain relief in the majority of patients. Since 1972 a further 55 cases have been treated and are described here. The criteria for assessment of results differ from those in previous reports.

Patients and Methods

Since 1972, 55 patients (aged from 50 to 78 years) have had pituitary ablation. In all cases the indication for operation was intractable pain due to metastases from carcinoma of the prostate. In 53 patients, 2 pellets of Yttrium^{90} were separately implanted into the pituitary fossa under radiographic screening, as described by Fergusson (1957). Each pellet contained between 3.5 and 4.9 millicuries of radioactivity. In a further 2 patients included in this series, 1 ml of alcohol only was instilled into the pituitary.

All patients had prior hormonal treatment: 35 with oestrogen, 3 with bilateral orchiectomy and 17 with a combination of both. When the disease became resistant to hormonal treatment, 23 had further attempts at palliation with cyproterone, aminoglutethimide hydroxyurea, bromoergocryptine and, more recently, a razoxane/cyclophosphamide/prednisone regime, or a combination of these. In 11 patients, relief of pain was attempted with localised deep X-ray therapy.

Criteria for Assessment

As pain was the indication for ablation in all cases, assessment of response was based on the use of subjective criteria. No attempt was made to use objective criteria such as testosterone levels (Robinson and Thomas, 1971) or growth hormone levels (Murphy *et al.*, 1971).

Fergusson and Hendry (1971) assessed their results by dividing the patients post-operatively into 3 groups: good response (complete pain relief), response (partial pain relief) and no response. In this report we are using the provisional criteria for pain relief based on analgesic requirements suggested by the British Prostate Group:

5—Parenteral narcotic analgesics.
4—Frequent oral narcotic analgesics.
3—Occasional oral narcotic analgesics.
2—Frequent non-narcotic analgesics.
1—Occasional non-narcotic analgesics.
0—No analgesics.

Results

The results following pituitary ablation are shown

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Table 1 Overall Response to Pituitary Ablation

Grade of pain	*Pre-operative assessment*	*Post-operative assessment*
5	1	0
4	34	7
3	4	7
2	16	11
1	0	18
0	0	12

$P < 0.001$.

in Table 1. Of the 55 patients, 39 (71%) needed narcotics pre-operatively. The remaining 16 patients (29%) took frequent non-narcotic analgesics. Post-operatively only 14 patients (26%) still needed narcotics to relieve their pain. A total of 12 patients (22%) were completely pain-free post-operatively and 18 patients (32%) needed occasional non-narcotic analgesics only.

Table 2 shows the different groups of patients according to their pre-operative assessment and the effect of pituitary ablation. It can be seen that there was some improvement in analgesic requirements in most patients, although in 2 cases the pain appeared to have got worse.

Of the 34 patients who required oral narcotics pre-operatively (group 4) only 11 (33%) still needed them post-operatively and 6 patients (18%) were able to decrease their narcotic intake. The remaining 23 patients (67%) were weaned off narcotics. The pain had been present pre-operatively for periods ranging from 1 to 58 months (mean duration 12.3 months). The satisfactory responses lasted either up to death or to within one month of it.

Table 2 Comparison of Pre- and Post-operative Pain Assessment

Pre-operative assessment (No. of patients in brackets)	*Post-operative assessment*					
	5	*4*	*3*	*2*	*1*	*0*
5 (1)	—	—	—	1	—	—
4 (34)	—	5*	6	7	7	9
3 (4)	—	—	1*	—	3	—
2 (16)	—	2*	—	3*	8	3
1 (0)	—	—	—	—	—	—
0 (0)	—	—	—	—	—	—

* Patients in each group who did not benefit from pituitary ablation.

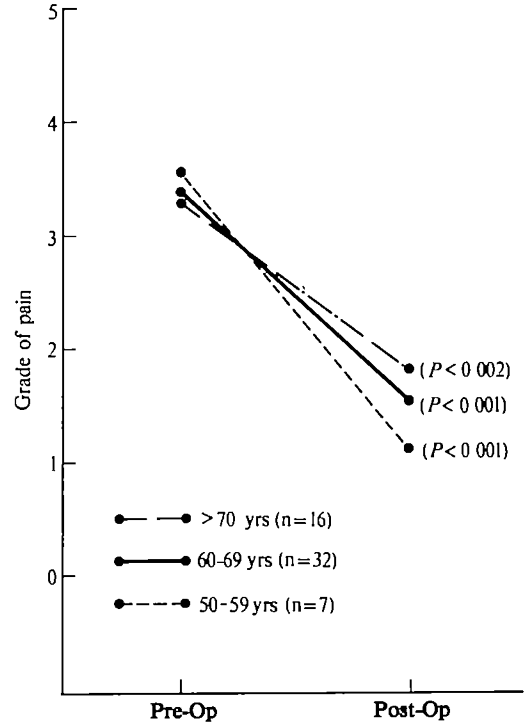

Fig. 1 Effect of age of patient on results.

Effect of Age of Patient on Results

The effect of the age of the patient on the result of pituitary ablation is demonstrated in Figure 1, where the points on the graph are the mean pre-operative and post-operative grades of pain, according to the above classification. In each age group there was considerable relief of pain post-operatively. However, although in each group there was a highly significant difference between the pre-operative and post-operative analgesic requirement, there was no significant difference between each group, and it could not therefore be said that any age group responded better than any other.

Effect of Duration of Disease on Results

Figure 2 shows the response to ablation with the patients grouped according to the duration of the disease pre-operatively. In those patients whose disease had been present for less than 12 months, 5 (50%) needed narcotics pre-operatively and 4 (40%) needed them post-operatively. When the disease had been present for more than 3 years, 15 patients (83%) needed narcotics pre-operatively and only 4 (22%) needed them post-operatively.

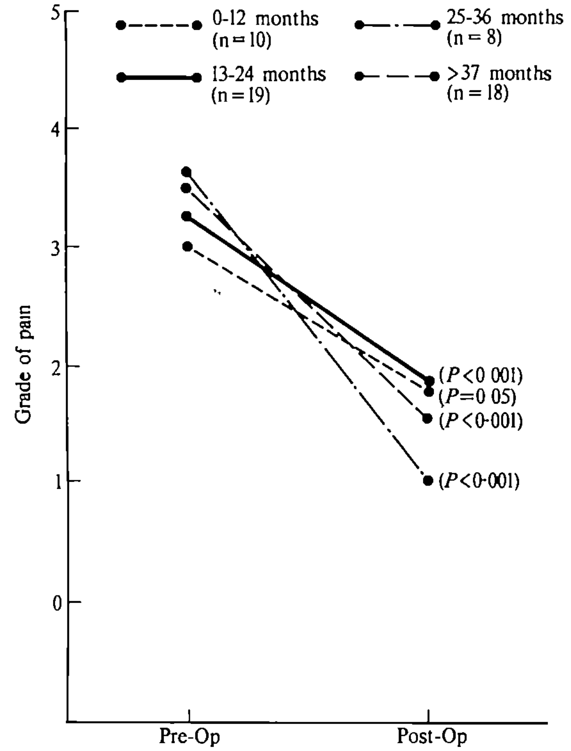

Fig. 2 Effect of duration of disease on results.

Although it would appear that there was a better response associated with longer duration of disease, there was no significant difference between the groups.

Effect of Previous Hormonal Treatment on Results

Figure 3 shows the mean pre-operative and post-operative grade of pain in 55 patients divided into 2 groups according to whether they originally responded (45 patients) or did not respond (10 patients) to previous hormonal manipulation. Of the 45 patients in the first group, 33 (73%) needed pre-operative narcotics and 11 (24%) needed them post-operatively. Of the 10 patients in the second group 6 (60%) needed pre-operative narcotics and only 3 (30%) needed them post-operatively. There is no significant difference of response between the 2 groups.

Complications

Diabetes insipidus occurred in 10 patients but was successfully treated in all cases with Pitressin snuff. Rhinorrhoea occurred in 5 cases but was temporary in all except one patient. Transient headache developed in 2 patients. Cranial nerve damage occurred in 6 patients: the third nerve was damaged in 2 patients, the fourth nerve in 2 patients, the third and fourth nerves together in one patient and the sixth nerve in one patient. Meningitis developed in one patient but this was successfully treated with antibiotics.

One patient became paraplegic and another died within the first 24 h, but in both cases the cause was considered to be the disease itself rather than the operation.

This incidence of complications compares favourably with that noted in previous reports.

Survival

Of the 34 patients taking frequent oral narcotics pre-operatively, the average length of survival in the responders was 20 weeks and in the non-responders 14½ weeks. The longest survivors were 2 patients who lived for 1½ and 2 years respectively. Both had multiple bony metastases but were pain-free.

Discussion

When palliation of pain rather than treatment of

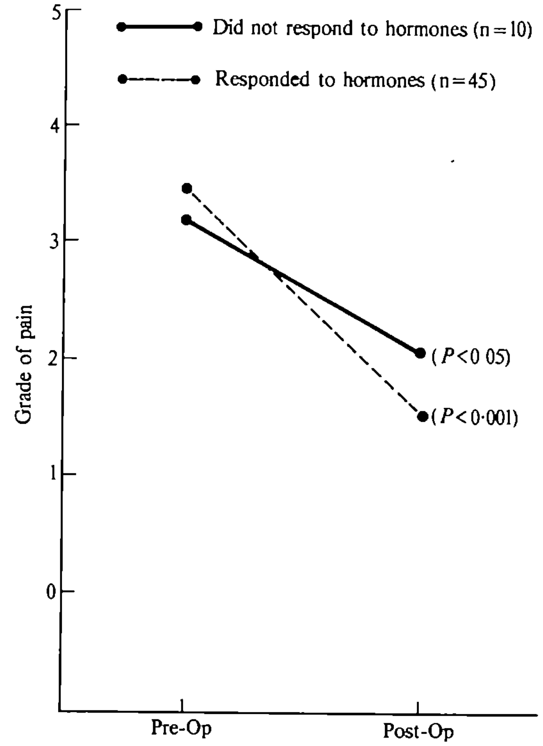

Fig. 3 Effect of previous hormonal therapy on results.

the disease becomes the major problem, the clinician must ask himself which form of therapy is the most valuable. Should he continue with strong analgesics which barely control the patient's pain and reduce the quality of life by psychomotor retardation, or should he use some other form of palliation, such as pituitary ablation, radioactive phosphorus (Johnson and Haynie, 1977), or chemotherapy (O'Donoghue *et al.*, 1980), all of which have been shown to be of value?

In the largest reported series, Fergusson and Phillips (1962) and Fergusson and Hendry (1971) have shown that pituitary ablation produces complete pain relief in about one-third of patients, some pain relief in another third, and no relief of pain in one-third. Other reports of smaller series have shown complete pain relief in about 50% (Straffon *et al.*, 1968; Morales *et al.*, 1971). Although we have used different criteria for assessing pain relief, it can be seen that 44 patients (80%) experienced significant relief of pain postoperatively; of these, 12 patients were completely pain-free. There was no pain relief in 11 patients (20%).

It was suggested in a previous report (Fergusson and Phillips, 1962) that absence of response to hormonal manipulation precluded a good result in pituitary ablation. In this series neither the age of the patient, the duration of the disease, nor prior response to hormonal therapy made any difference to the response to pituitary ablation. It appears that pituitary ablation is capable of causing a remission in patients who did not previously respond to hormones, or who eventually relapsed on hormonal treatment.

There is no doubt that ablation of the pituitary with radioactive Yttrium has an important place in the treatment of advanced carcinoma of the prostate. It is a relatively simple, short surgical procedure with a low complication rate and produced significant relief of pain in 80% of patients in this series.

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Urethral Diverticulum in Females

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Summary—Thirteen cases of urethral diverticulum in females are reported. Symptoms were non-specific. Two cases presented with suppuration in previously undiagnosed diverticula.

The most important physical sign was palpation of the sac on vaginal examination. Micturating cystourethrography was the most useful investigation.

An association with carcinoma makes excision mandatory and in 10 cases this was performed by a vaginal approach. A laterally based flap incision is described which was used in 7 cases without complication. In one case the diverticulum recurred after 5 years and was removed in the same way.

Two cases that presented with suppuration were treated by incision and drainage: in one the diverticulum re-formed and the other case was lost to follow-up.

The aetiology of the condition is unknown but we believe, on histological evidence, that it is congenital.

Our experience of urethral diverticulum has led us to believe that some features of the condition have been neglected and its management has often been unsatisfactory. In this paper we draw attention to these features and describe a new approach for the excision of these diverticula.

Patients

Thirteen patients with a urethral diverticulum have been seen and treated at the London Hospital during the past 11 years.

The presenting features are summarised in Table 1. Two patients presented with infection in previously undiagnosed diverticula. Both were nearing the end of a pregnancy. One of them, a known heroin addict, had suffered with recurrent urinary tract infections; the other was previously symptom-free and had had an uncomplicated pregnancy and delivery 2 years earlier. At operation in each case a little pus could be expressed from the sac, and both were incised and drained into the vagina. Four years later one (Case 2) re-presented with a vaginal swelling that filled during micturition and had to be manually expressed to prevent dribbling incontinence.

Two other cases also presented with vaginal swellings (Cases 4 and 10). One of these had no urinary symptoms and the diverticulum was a chance finding during pregnancy. The other had urgency.

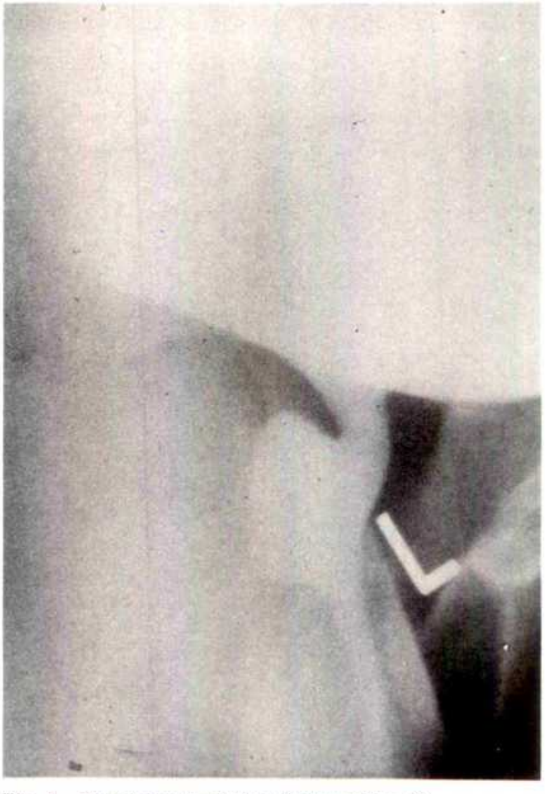

Fig. 1 Female urethral diverticulum (Case 6).

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Table 1 Presentation of 13 Cases of Urethral Diverticulum, 1968-1978

Case no.	*Age*	*Parity*	*Symptoms*	*Vaginal signs*	*Notes*
1	25	1	Suppuration	Abscess	Heroin addict pregnant
2	18	2	Suppuration	Abscess	Pregnant
Re-presented	22	3	Vaginal swelling	Cystic swelling	
3	55	6	Stress incontinence dysuria	Cystic swelling	Previous colporrhaphy
4	31	3	Vaginal swelling	Cystic swelling	
5	44	3	Multiple u.t.i.	Cystic swelling	
Recurred	49	3	Dysuria and frequency	Not recorded	
6	35	5	Haematuria	None	
7	41	7	Stress incontinence dysuria	Stones palpable	Stones in diverticulum
8	73	1	Stress incontinence	Tumour palpable	Stones + tumour in diverticulum
9	37	5	Dysuria	None	
10	30	1	None	Cystic swelling	Refused surgery
11	60	2	Multiple u.t.i.	Cystic swelling on e.u.a.	
12	36	0	Multiple u.t.i. urgency	none	
13	39	2	Dysuria and incontinence	Cystic swelling	

The remaining 9 patients presented with urinary symptoms. In 6 of them an abnormality could be felt on vaginal examination, though in one case only under anaesthesia.

X-ray Findings

In the 7 cases in which it was performed, a micturating cystourethrogram clearly demonstrated the diverticulum (Fig. 1). In Case 7, 4 stones within the diverticulum were seen overlying the symphysis on the plain film. In Case 8, which ultimately was found to have a carcinoma in the diverticulum, a urethral stone was seen on the plain film, and there was a filling defect at the bladder base on the intravenous urogram.

In only one case was a urethrogram performed and it showed the diverticulum well. In no case did the intravenous urogram show a diverticulum of the urethra.

Table 2 Treatment of 13 Cases of Urethral Diverticulum

Case no.	*Orifice*	*Operation*	*Result*	*Follow-up*
1		Incision and drainage	Healed	Lost
2		Incision and drainage	Healed	
Re-presented	Midline	Excision (lateral flap)	Healed	6 months
3		Excision (midline incision)	Fistula and secondary repair	1 year then lost
4	Midline	Excision (midline incision)	Healed	3 months then lost
5	Midline	Excision (lateral flap)	Healed	
Recurred		Excision (lateral flap)	Healed	Lost
6	Midline	Excision (lateral flap)	Healed	3 years
7	Midline	Excision (lateral flap)	Healed	6 months
8	Midline	Urethrectomy + urethroplasty	Incontinent	Tumour recurred
9	Midline	Excision (lateral flap)	Healed	1 month
10		Refused		
11	Left posterior	Excision (midline incision)	Healed	1 month
12	Midline	Excision (combined approach)	Healed eventually	18 months
13	Midline	Excision (lateral flap)	Healed	3 months

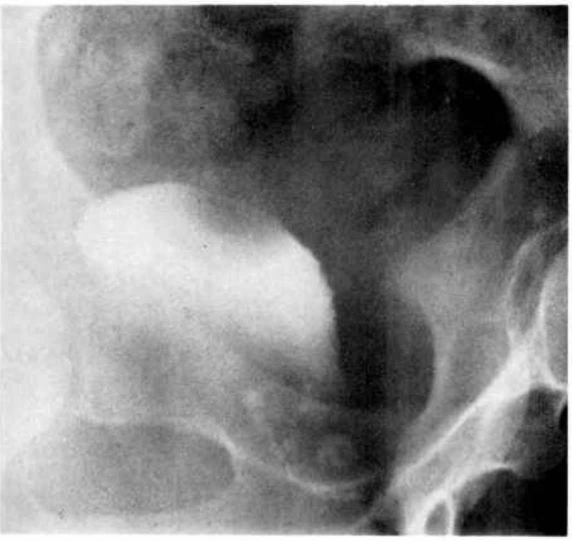

Fig. 2 Large female urethral diverticulum extending up to the right ureter (Case 12).

Urethroscopy

One patient (Case 10) refused all surgery. In 10 cases without infection and in one recurrence, urethroscopy was performed. In 9 (including the recurrence), the opening of the diverticulum was seen in the midline posteriorly, and in one case it was on the left. In one patient (Case 3) no orifice was seen, but Bonney's blue instilled into the urethra was later found in the diverticulum and a small midline orifice was identified. In Case 8 a papillary tumour was seen arising within the diverticulum and almost filling the urethra.

Operations

The operations performed are shown in Table 2. The 2 cases with suppuration underwent incision and drainage into the vagina. The heroin addict failed to attend for follow-up, but at the time of discharge had no urethral fistula. The second case had a urethrovaginal fistula that healed spontaneously.

Case 8 was a frail woman of 73 years. Her diverticulum contained an adenocarcinoma and it was this that required treatment rather than the diverticulum itself. Local urethrectomy and urethroplasty were performed but there was local recurrence and she has since undergone more radical surgery.

Case 10 had a diverticulum that was symptomless and found on routine examination during pregnancy. Diverticulectomy was planned, but she refused surgery.

Case 12 had by far the largest diverticulum and yet was the most difficult to diagnose and treat. She had symptoms of urgency, frequency, occasional urge incontinence and recurrent urinary tract infections. There was nothing to find on examination and intravenous urography was normal. She was examined under anaesthesia and particular care was taken over the urethra, but no orifice was seen. As her symptoms persisted she had a micturating cystourethrogram which showed a large diverticulum extending to the right behind the bladder and ureter (Fig. 2). At a second urethroscopy an orifice was seen in the midline posteriorly. The diverticulum was excised by a combined approach through the vagina and a Pfannenstiel incision.

Ten cases, including 2 recurrences, were treated by excision of the sac and primary closure of the urethral defect. In Case 12 the diverticulum was shaped like a dumb-bell with extensions up to the bladder neck on either side, but even so it was easily removed by this route. In 2 early cases the incision was made in the midline of the vagina, but one developed a urethrovaginal fistula which required further surgery. In the patient with the urethral opening on the left side, the same approach was used without complication.

With the usual midline opening we now use a technique involving a laterally based vaginal flap incision illustrated by Case 7.

Operative Technique

Plain X-ray had shown that there were stones in the sac and they could be seen through the orifice in the posterior wall of the urethra with the urethroscope. At operation a rectangular flap, based laterally, was raised (Fig. 3a) to reveal the diverticulum (Fig. 3b). It was opened and excised (Fig. 3c). The small opening in the urethra (Fig. 3d) was closed with interrupted Dexon (Fig. 3e). The vaginal flap was closed over the urethra with Dexon and the vagina was packed with gauze (Fig. 3f). A catheter was left indwelling for 10 days. Healing was uncomplicated. One month later she had lost her symptoms of stress incontinence and dysuria, was voiding naturally and had no infection.

Results

Eight of 10 cases treated by simple diverticulectomy have done well. The 2 poor results were a

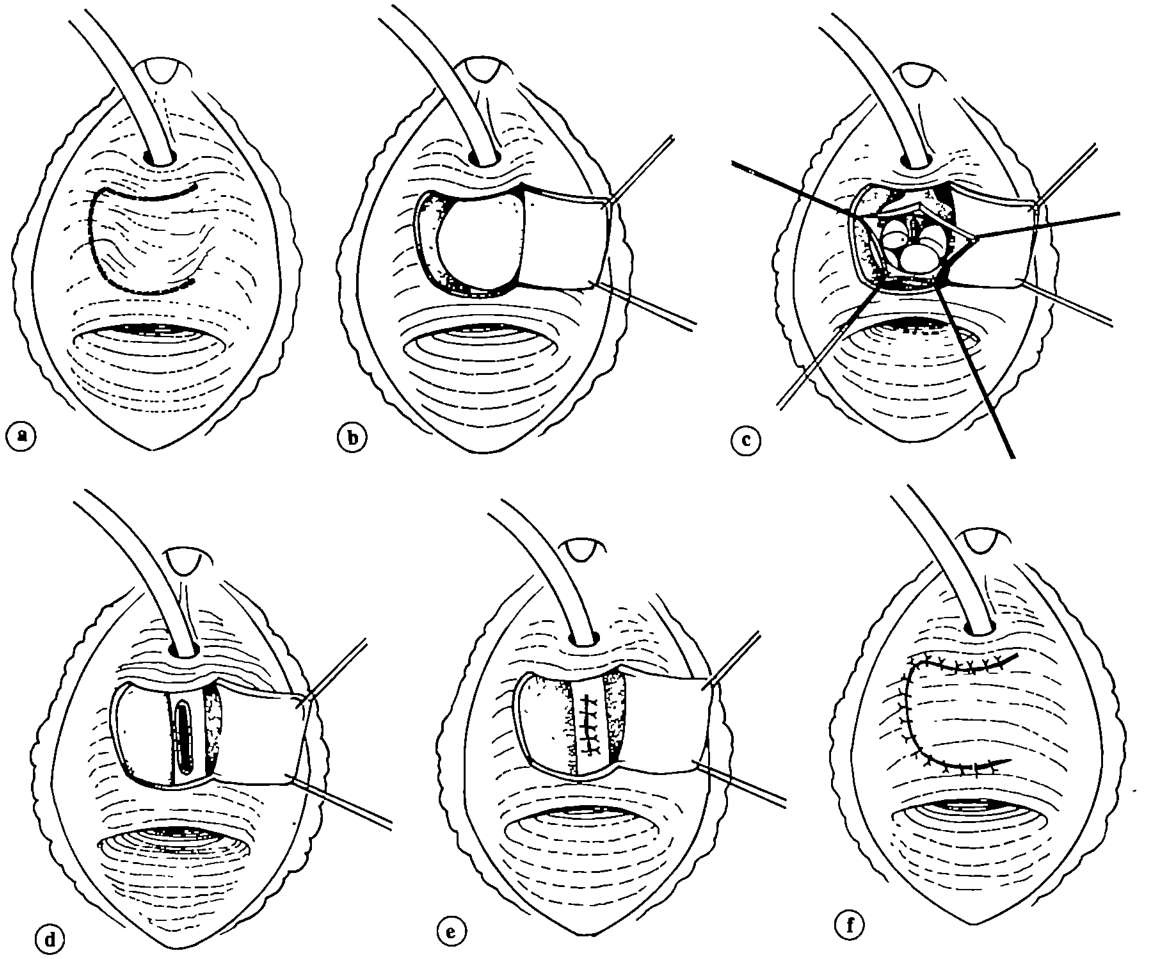

Fig. 3 (a) Incision in the anterior wall of the vagina (a catheter has been passed into the urethra). (b) The vaginal flap has been raised to reveal the diverticulum. (c) The diverticulum has been opened and 4 stones are seen inside. (d) The sac has been removed and the small opening into the urethra is left. (e) Closure of the urethra. (f) Closure of the vaginal flap.

urethrovaginal fistula in a patient who had a midline vaginal incision, and a recurrence of the diverticulum after 5 years in another patient.

Case 12, with a very large diverticulum excised by a combined approach, was left incontinent and later required excision of redundant urethral tissue. Thereafter she improved but her bladder, which was normal after the first operation, developed unstable detrusor contractions; she remains wet in the afternoons and at night.

Pathology

Material from 11 cases (including both recurrences) was available and the findings are summarised in Table 3. The walls of all the specimens contained smooth muscle in addition to fibrous tissue, suggesting a congenital rather than an acquired origin.

In Case 8 the mucosa was part squamous, part transitional and the tumour was an adenocarcinoma with a well differentiated papillary component. There was deep invasion of the diverticular wall. In the subsequent recurrence both patterns of tumour were seen.

The re-formed sac in Case 2 was similar to the other specimens. In Case 5, however, it is not possible to say whether the recurrent diverticulum was of urethral or vaginal origin.

Discussion

Urethral diverticula are not rare (Newland *et al.*,

Table 3 Pathological Findings in 11 Resected Specimens of Urethral Diverticulum

Case no.	*Epithelium*	*Ulceration*	*Inflammation*	*Notes*
2R	Squamous	No	Severe, chronic	
3	None		Mild, acute + chronic	
4	Transitional	Yes	Little, mainly acute	
5R	Mixed	No	Mild, acute + chronic	
6	Transitional	Yes	Mild, acute + chronic	Squamous metaplasia
7	Squamous	No	Mild, acute + chronic	Stones in sac
8	Mixed	No	None	Adenocarcinoma in sac
9	Transitional	Yes	Moderate, acute + chronic	
11	Transitional	Yes	Moderate, chronic	Squamous metaplasia foci of calcification
12	Squamous	Yes	Little	
13	Squamous	Yes	Moderate, acute + chronic	

R = recurrent case.

1970; Roberts and Smith, 1976) and increasing awareness of the condition has led to more frequent diagnosis (Davis and Telinde, 1958). We have found that the diagnosis can most often be made on careful vaginal examination and this must not be neglected when assessing the female urinary tract. Micturating cystourethrography is the most useful investigation to confirm the diagnosis. Symptomless cases have been reported (Andersen, 1967). The occurrence of stones in 2 of our cases (one of which also had a carcinoma) and of focal calcification in another is unusual (Ward *et al.*, 1967).

It is a moot point whether such diverticula are truly congenital and perhaps allied to the very uncommon paraurethral cysts (Blaivas *et al.*, 1976) or whether they arise by epithelialisation of a paraurethral abscess. In 9 of our primary cases with histology available the presence of muscle in the wall suggests a congenital origin.

The aetiology of the re-formed and recurrent cases is obviously different. In the one (Case 2), the diverticulum became infected and was incised; when the resulting fistula healed, the diverticulum only re-formed. In the other, classification is difficult; it may represent an incomplete removal, partial healing of an unrecognised urethrovaginal fistula or a completely new cyst. Cases of 2 symptomless diverticula in the urethra have been reported (Andersen, 1967).

The extension of the diverticulum beside the right ureter in Case 12 and to either side of the bladder neck in Case 13 raises the possibility that they were not the same condition as the others. They might represent partially obliterated ectopic ureters (Davis and Telinde, 1958).

Carcinoma of the urethra is uncommon and the majority are of squamous cell origin (Desai *et al.*, 1973). The report by McLoughlin (1975) of a case of carcinoma *in situ* in a urethral diverticulum and the presence of frank carcinoma in one of our cases are, therefore, significant: these experiences argue strongly in favour of excision of the sac. The difficulty of dissection and the risk of a urethrovaginal fistula have led some surgeons to advocate simple marsupialisation alone (Spence and Duckett, 1970), but this may lead to so short a urethra that the patient is made incontinent.

We have found that the laterally based flap incision in the anterior vaginal wall makes full exposure of the diverticulum easy and covers the urethral defect with intact vaginal wall. The dissection has not proved difficult even in the recurrent case. Using this technique we have had no delayed healing, fistulae or incontinence.

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48-Hour Cephradine and Post-prostatectomy Bacteriuria

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Summary—In a randomised, controlled trial of intramuscular cephradine given in a dose of 1 g 6-hourly for 48 h, there was a significant reduction in the incidence of significant bacteriuria after transurethral resection. In contrast, the incidence of significant bacteriuria after open prostatectomy was unchanged. Post-operative complications were reduced in patients who received cephradine. The use of short-term cephradine would appear to be justified.

It is known that up to 24% of patients may have bacteriuria before prostatectomy and this percentage is greater in catheterised patients (Jackaman and Chisholm, 1975). Infected urine may lead to serious and sometimes fatal complications such as secondary haemorrhage, pyelonephritis and septicaemia (Miller *et al.*, 1958). The incidence of infection has been reduced by the use of a closed system drainage (Gillespie *et al.*, 1967) and also by the use of frusemide (Essenhigh *et al.*, 1970) and prophylactic antibiotics (Hills *et al.*, 1976). In our unit at the Western Infirmary, Glasgow, we found that either co-trimoxazole or cephradine was the most useful antibiotic as judged by analysis of all urine sensitivities from the unit over a 6-month period. It was decided to evaluate a 48-h course of intramuscular cephradine by means of a prospective controlled trial in all men undergoing prostatic surgery. We chose cephradine because of the ease of administration parenterally compared with cotrimoxazole.

Patients and Methods

All patients undergoing open or transurethral prostatectomy were included in this study. Patients known to have significant pre-operative infection and patients on antibiotics were excluded. In many cases, however, a patient had infection at the time of operation but this was not known until afterwards. Such patients are included in the analysis because it is important to know the effect of an antibiotic regime in these cases. Patients allergic to penicillin or cephalosporins were excluded. Patients with a serum creatinine greater than 140 mmol/l were also excluded.

Randomisation was stratified to give equal numbers of patients in 4 groups: (1) patients with pre-operative catheter drainage undergoing open prostatectomy (OP); (2) patients without a catheter undergoing open prostatectomy; (3) patients with a pre-operative catheter undergoing transurethral resection (TUR); (4) patients without a pre-operative catheter undergoing transurethral resection.

Cephradine 1 g was given intravenously with the induction of anaesthesia and then intramuscularly every 6 h for 48 h to a total of 8 g. Although the technique of operation was standardised, the operations were performed by different surgeons. Two 20 mg injections of frusemide were given in the first 24 h to promote diuresis. Urethral catheters were allowed to drain into a closed collecting system. Irrigation was undertaken only when required and sterile water used. No local antibacterial agents were used. The catheters were removed as soon as signs of fresh bleeding ceased.

Data on the patients' clinical progress were recorded daily. Urine samples were examined daily from the day of admission until discharge or 9 days post-operatively. Either a midstream specimen or, in the presence of a catheter, a specimen aspirated from the catheter tubing, was examined. All of the samples were collected at 7 a.m. and refrigerated at 4° centrigrade within minutes of collection. They were all cultured within 3 hours of collection and examined by the same indepen-

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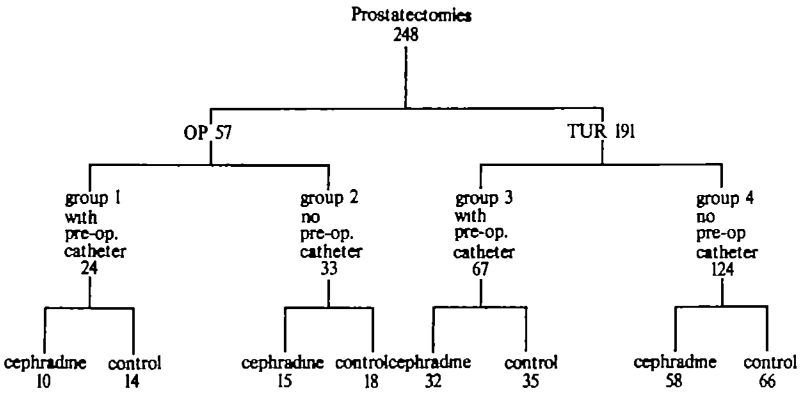
Prostatectomies
248
OP 57
TUR 191
group 1 with pre-op. catheter 24
group 2 no pre-op. catheter 33
group 3 with pre-op. catheter 67
group 4 no pre-op catheter 124
cephradine 10
control 14
cephradine 15
control 18
cephradine 32
control 35
cephradine 58
control 66

Fig. Distribution of patients by operation and presence of pre-operative catheter drainage.

dent examiner. Significant bacteriuria (SB) was defined as 10^5 or more organisms per ml of urine. Pyuria was not included in the criteria for diagnosis of infection because of the inevitable presence of white cells in the urine following surgery.

Open prostatectomy wounds were examined by the same independent examiner on post-operative days 5 and 8. The wounds were classified into 4 grades on the basis of clinical assessment and the results of cultures: (1) severe wound infection: purulent discharge, culture positive for potential pathogens; (2) mild wound infection: erythema, scanty pus, cultures positive; (3) colonised wound: not clinically infected, cultures positive; (4) healed wound: cultures negative (Griffiths *et al.*, 1976).

Results

Two hundred and forty-eight patients entered the trial (Fig.). The median age of the patients was 69 years (range 46 to 93 years). A similar age distribution was attained in all groups, indicating that there was satisfactory randomisation. No patient who received cephradine developed a hypersensitivity reaction. At the time of operation all of the patients in the trial were thought by the urologist to have sterile urine. However, overnight cultures of the pre-operative sample often showed the patient to have had significant bacteriuria at the time of the operation (Table 1) and this was more often the case in the presence of a pre-operative catheter ($\chi^2 = 17.4$; $P<0.001$).

Two distinct groups of patients were considered: Group A patients, who had pre-operative sterile urine and in whom the use of cephradine was prophylactic, and Group B patients, who had pre-operative significant bacteriuria (Table 3).

There was no significant reduction in post-operative significant bacteriuria in patients who underwent open prostatectomy and who received cephradine. In patients who underwent transurethral resection the overall incidence of post-operative significant bacteriuria was significantly reduced in patients receiving cephradine (Table 2). There was a reduction even in the presence of pre-operative significant bacteriuria in whom the use of cephradine must be considered therapeutic although not guided by sensitivity studies (Table 3).

A measure of the strength of the effect of an antibiotic in reducing the incidence of post-operative significant bacteriuria is given by the

Table 1 Incidence of Pre-operative Significant Bacteriuria in Relation to Pre-operative Catheter Drainage

	Number of patients	*Number (%) with pre-operative significant bacteriuria*	*Number with pre-operative sterile urine*
Open prostatectomy and transurethral resection			
With pre-operative catheter	91	40 (44)	51
Without pre-operative catheter	157	29 (18)	128
Total	248	69 (28) (Group B)	179 (Group A)

Table 2 Incidence of Post-operative Significant Bacteriuria According to Type of Prostatectomy

	Number of patients	*Number (%) developing post-operative significant bacteriuria*	*Number with post-operative sterile urine*	
Open prostatectomy				
Cephradine	25	11 (44)	14	$P = 0.8$
Control	32	15 (47)	17	
Transurethral resection				
Cephradine	90	19 (21)	71	$P = <0.001$
Control	101	49 (49)	52	

relative risk. For Group A patients the risk of developing post-operative significant bacteriuria when no antibiotic is given is 5.7 times greater than when cephradine is given. For Group B patients this figure is 2.8. This would indicate that the antibiotic is more effective in preventing significant bacteriuria in the group receiving it prophylactically.

The genera of organisms appeared to be the same whether open prostatectomy or transurethral resection had been performed, and whether or not cephradine had been administered (Table 4). Further details of the organisms and their antibiotic sensitivities will be published elsewhere (Williams, in preparation).

The overall incidence of complications is shown in Table 5. No patient receiving cephradine developed either bacteriaemic shock or orchitis.

In patients with no post-operative significant bacteriuria, the incidence of other post-operative complications was reduced from 13 to 5% by the administration of cephradine ($P = 0.06$), as shown in Table 6. In addition, patients developing post-operative significant bacteriuria, despite cephradine administration, still had a reduced incidence of other immediate post-operative complications ($P = 0.04$).

"Incontinence" was defined as incontinence lasting more than 24 h after removal of the catheter and in most cases this resolved after a few days. Seven patients died, 5 in the control group and 2 in the cephradine group. The deaths were due to myocardial infarction (4), cerebrovascular accident (2) and one unrelated malignancy.

Serum creatinine and urea were measured preoperatively and on the fifth post-operative day. There was no evidence in this trial that cephradine added to impaired renal function. Cephradine made no difference to the duration of hospital stay except in open prostatectomy patients with pre-operative catheter drainage. These patients had the highest incidence of post-operative wound

Table 3 Incidence of Post-operative Significant Bacteriuria in Group A (Pre-operative Sterile Urine) and Group B (Pre-operative Significant Bacteriuria) Patients According to the Type of Prostatectomy

	Number of patients	*Number (%) developing post-operative significant bacteriuria*	*Number with post-operative sterile urine*	
Open prostatectomy				
Group A				
Cephradine	18	6 (33)	12	$P = 0.6$
Control	26	11 (42)	15	
Group B				
Cephradine	7	5 (71)	2	$P = 0.9$
Control	6	4 (67)	2	
Transurethral resection				
Group A				
Cephradine	59	7 (12)	52	$P = <0.001$
Control	76	33 (43)	43	
Group B				
Cephradine	31	12 (39)	19	$P = 0.10$
Control	25	16 (64)	9	

Table 4 Genera of Organisms Isolated from Patients with Post-prostatectomy SB According to Type of Operation

	Open prostatectomy				*Transurethral resection*			
	Total		*Cephradine No.*	*Control No.*	*Total*		*Cephradine No.*	*Control No.*
	No.	*(%)*			*No.*	*(%)*		
Genus								
Enterococci	10	30	6	4	25	28	5	20
Esch. coli	5	15	3	2	21	24	8	13
Proteus species	5	15	2	3	15	17	5	10
Coagulase-negative Staphylococci	5	15	2	3	8	9	0	8
Klebsiella—Enterobacter species	4	12	2	2	11	12	3	8
Staph. aureus	3		0	3	2		0	2
Others	1		1	0	7		3	4
Number of isolates	33				89			
Number of mixed infections	7				15			
Number of patients with post-operative SB	26				68			

Table 5 Immediate Post-operative Complications

	Control	*Cephradine*
After OP and TUR	(N = 133)	(N = 115)
Significant bacteriuria	64	30
Bacteriaemic shock	2	0
Orchitis	3	0
Re-catheterisation	8	1
Incontinent	6	1
Re-operation	2	1
After open prostatectomy	(N = 32)	(N = 25)
Wound infection (grades I and II)	6	3

infection and consequently administration of cephradine shortened their post-operative in-patient stay.

Discussion

In this study the normal admission and handling of patients was not altered to suit a trial protocol. This is important as it means that the results are applicable to a general urology unit. Randomisation was stratified to allow for the higher pre-operative infection rate accompanying pre-operative catheterisation. When evaluating the results, distinction was made between the patients with sterile urine pre-operatively and those with an unknown infection. Previous trials have either excluded infected cases (Hills *et al.*, 1976) or failed to distinguish between the 2 groups (Genster and Madsen, 1970).

The risk of infection begins at the moment the catheter is inserted into the bladder and ends at a much less well defined time after the catheter is removed (O'Grady, 1972). We decided to administer cephradine for 48 h beginning at the time of operation. This is prophylaxis in Group A patients and a short course of therapy in Group B patients. Charlton *et al.* (1970) have shown that an antibiotic effective against the organism responsible for urinary infection sterilised the urine in 48 h and that, in general practice, a short course of antibiotics was as successful as a 10-day course (Charlton *et al.*, 1976). Previous trials of antimicrobial prophylaxis in prostatectomy patients have used longer periods of cover; for

Table 6 Incidence of Post-operative Complications According to the Presence of Post-operative SB

	Patients with post-operative SB		*Patients without post-operative SB*	
	No.	*No. (%) with at least one other immediate post-operative complication*	*No.*	*No. (%) with at least one immediate post-operative complication*
Cephradine	30	2 (7)	85	4 (5)
Control	64	13 (20)	69	9 (13)

example, Hills *et al.* (1976) used a 10-day course of co-trimoxazole, Gonzalez *et al.* (1976) a 10-day course of cephalothin and Lacy *et al.* (1971) a 3-24 day course of cephaloridine.

Strachan *et al.* (1977) found that cephazolin given as a single pre-operative dose reduced the incidence of post-operative wound sepsis in patients undergoing routine cholecystectomy. We found that the number of wound infections was reduced in patients receiving cephradine.

There were no serious side effects from cephradine. We found no cases of allergic rash. Cephaloridine has been shown to cause nephrotoxicity and this is enhanced by frusemide (Lawson *et al.*, 1970). We found no case of deteriorating renal function in patients given cephradine despite the concurrent use of frusemide. This was true even when pre-operative creatinine was elevated.

Large numbers are needed in order to produce statistically significant differences in morbidity and mortality, but the results of this trial indicate that a short-term course of antibiotics—in this case cephradine—does reduce the incidence of immediate post-prostatectomy complications.

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Hydroxyurea in the Management of Chronic Urea-splitting Urinary Infections

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Summary—The aim in the management of struvite stones is to remove all of the stones and to treat urinary infection. The bacterial species which are known to cause struvite stones produce the enzyme urease, which increases urinary pH by splitting urea and consequently causes urinary supersaturation with respect to struvite and hydroxyapatite.

The use of bacterial urease inhibitors with antibiotics is a new and interesting aid in the management of chronic urea-splitting infections. We describe our experience with the use of hydroxyurea in 15 patients with chronic urea-splitting infections.

Urinary stones caused by infection account for 15 to 20% of all urinary stones (Griffith, 1978a).

The bacterial species which play a fundamental role in the formation of infective stones produce the enzyme urease (Griffith *et al.*, 1976), which increases urinary alkalinity and the concentration of bicarbonate and ammonia ions by splitting urea and supersaturating urine with respect to struvite (Elliot *et al.*, 1958, 1959). In this way crystallisation occurs and stones form.

Thus a cycle is established between urea-splitting infection and struvite stones, because stones make it difficult to eradicate infection and the infection increases the risk of stone formation.

The management of infective stones should be directed towards (1) a complete surgical clearance whenever possible (Smith and Boyce, 1968); (2) medical therapy to reduce stone formation when surgery is contraindicated, and (3) the prevention of stone formation in high risk patients, *i.e.* patients with chronic urinary infection from urea-splitting organisms without any removable cause of urinary stasis. The use of urease inhibitors (Kobashi *et al.*, 1962; Griffith and Musher, 1973; Griffith, 1978b; Griffith *et al.*, 1978; Smith, 1978) with antibiotics may achieve urinary sterilisation or, at least, acidification in these patients.

In 1962 Kobashi *et al.* described the urease-inhibiting activity of hydroxamic acid. Experimental work had demonstrated the efficacy of hydroxamic acid in preventing both stone formation (Griffith and Musher, 1973) and pyelonephritic changes (Aronson *et al.*, 1974) usually induced by *Proteus* urinary infection. Griffith (1978a) and Griffith *et al.* (1978) also referred to the usefulness of hydroxamic acid in the management of patients with recalcitrant urea-splitting infections and renal stones. Unfortunately, hydroxamic acid is not easily available in most parts of the world. Although hydroxamic acid seems to have the greatest pharmacological potential of the hydroxamates (Fishbein and Daly, 1970), even hydroxyurea, which is easily available, shows a considerable urease-inhibiting power (Fishbein and Carbone, 1965; Smith, 1978). Smith (1978) referred to the use of hydroxyurea in infective stone patients.

The purpose of this paper is to present the results of hydroxyurea administration in patients with struvite stones when surgical removal was contraindicated, or in patients with residual or previous stones or chronic urea-splitting infection or both and with a high risk of stone growth or new stone production.

Material and Methods

Fifteen patients with chronic urea-splitting urinary infection entered the trial (Table).

All patients had already been treated with repeated courses of antibiotics; sterilisation could not be achieved in 11 cases and urinary infection recurred after a short time in 4.

Two patients (cases 11 and 12) had bilateral

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Table Patients in the Trial

Patient	*Age*	*Disease*	*Bacterial species*	*Duration of treatment (days)*	*Associated therapy*
(1) M.Q.	48	Chronic urinary tract infection (UTI)	*Proteus rettgeri*	40	Nitrofurantoin
(2) C.D.	68	Chronic UTI	*Proteus rettgeri*	60	Nitrofurantoin
(3) S.B.	65	Chronic UTI	*Proteus mirabilis*	15	Nitrofurantoin
(4) C.B.	12	Colonic conduit	*Proteus morgani*	21	Carbenicillin
(5) B.F.	52	Chronic UTI	*Proteus mirabilis*	15	Nalidixic acid
(6) A.V.	45	Chronic UTI	*Proteus rettgeri*	45	Tobramycin (15 mg) + Co-trimoxazole (15 mg)
(7) R.A.	23	Chronic UTI	*Proteus morgani*	60	Co-trimoxazole
(8) D.M.	48	Previous pyelolithotomy, chronic UTI	*Proteus rettgeri*	30	Nalidixic acid
(9) M.G.	16	Previous nephrolithotomy, chronic UTI	*Pseudomonas aeruginosa*	60	Co-trimoxazole
(10) R.C.	55	Previous vesicolithotomy, chronic UTI	*Proteus rettgeri*	15	Tobramycin
(11) T.M.	74	Bilateral staghorn calculi	*Proteus mirabilis*	Up to date	Carbenicillin
(12) F.S.	71	Bilateral staghorn calculi	*Proteus mirabilis*	Up to date	Nitrofurantoin
(13) C.A.	65	Caliceal stone in polycystic kidney	*Proteus rettgeri*	Up to date	Nitrofurantoin
(14) P.V.	53	Ileal ureter: caliceal stone	*Proteus rettgeri*	Up to date	Oxolinic acid
(15) D.E.	52	Residual stone in horseshoe kidney	*Proteus rettgeri*	Up to date	Nitrofurantoin

staghorn calculi and were considered too ill for surgical intervention; one patient (case 13) had a small caliceal stone in a polycystic kidney; one patient (case 14) developed a small caliceal stone after ileoureteroplasty for ureteric neoplasm; one patient (case 15) had a small residual stone in a horse-shoe kidney. Three patients (cases 8, 9 and 10) had persistent urinary tract infection after surgical removal of the stones and 7 patients had had positive urine cultures for urea-splitting organisms for at least one year, despite treatment.

All patients were given hydroxyurea 500 mg in the morning and a culture-specific antibiotic. If tests showed complete resistance of the isolated bacteria, as in cases 1, 2, 3, 12, 13 and 15, nitrofurantoins were administered.

A urinary output exceeding 2 litres/24 h was maintained in every patient. The patients were instructed to measure and record their urinary pH by means of test strips in a freshly voided specimen every morning before taking hydroxyurea.

A complete blood count, an automated serum biochemical profile and urine cultures were obtained every week during treatment with hydroxyurea.

Length of follow-up ranged from 5 to 9 months.

Results

No toxic effects were found in any of the patients studied; neither bone marrow depression nor altered liver or renal function was revealed by routine controls and white blood cells showed little, if any, decrease (Fig. 1).

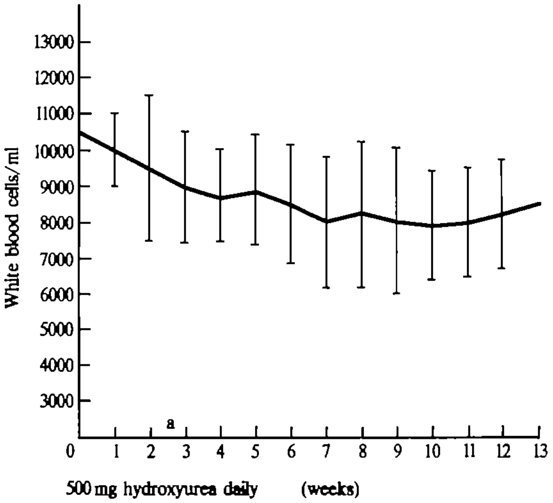

Fig. 1 Mean change in white blood cells during administration of hydroxyurea.

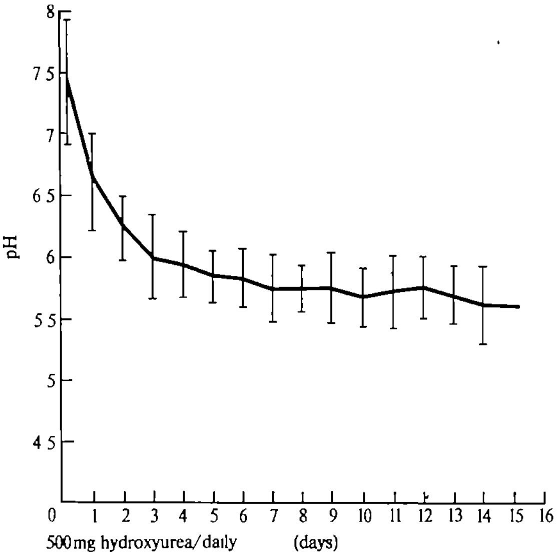

Fig. 2 Mean urinary pH modification during administration of hydroxyurea (patients without stones).

Results were evaluated in 2 groups:

Group 1: patients without stone (cases 1 to 10).
Group 2: patients with stone (cases 11 to 15).

Urinary acidification was achieved in all patients in group 1 after one day's treatment (Fig. 2) and remained between 5.3 and 6.5 for the whole course of treatment. Urinary pH (Fig. 3) returned acid levels after 2 to 3 days' treatment in only 3 out of 5 patients in group 2. In the other 2 patients it was necessary to increase the dose of hydroxyurea to 1 g daily in 2 doses (Fig. 3).

The increased dose caused no side effects and produced urinary acidification within 3 days.

In group 1 sterile urine was obtained in 9 out of 10 patients after a variable delay (Fig. 4); therapy was stopped after 2 consecutive negative cultures. Although kept under periodic cultural control thereafter, none experienced a recurrence of infection.

Post-operative follow-up ranged from 3 to 7 months.

In one patient (case 7), periodic culture of urine during therapy showed that a growth of *Pseudomonas aeruginosa*, which was not urea-splitting, had replaced the pre-treatment *Proteus* strain. This patient was then excluded from the trial after 3 weeks with acid urine and given carbenicillin.

In group 2 sterilisation of the urine was not achieved. One patient (case 14) showed a negative urine culture after one month's therapy but infection recurred a week later, although hydroxyurea administration has been continued.

All patients in group 2 were then introduced into a long-term trial with nitrofurans and hydroxyurea. At present their follow-up ranges from 4 to 9 months.

The size of renal stones is periodically assessed by means of standard X-ray of the abdomen

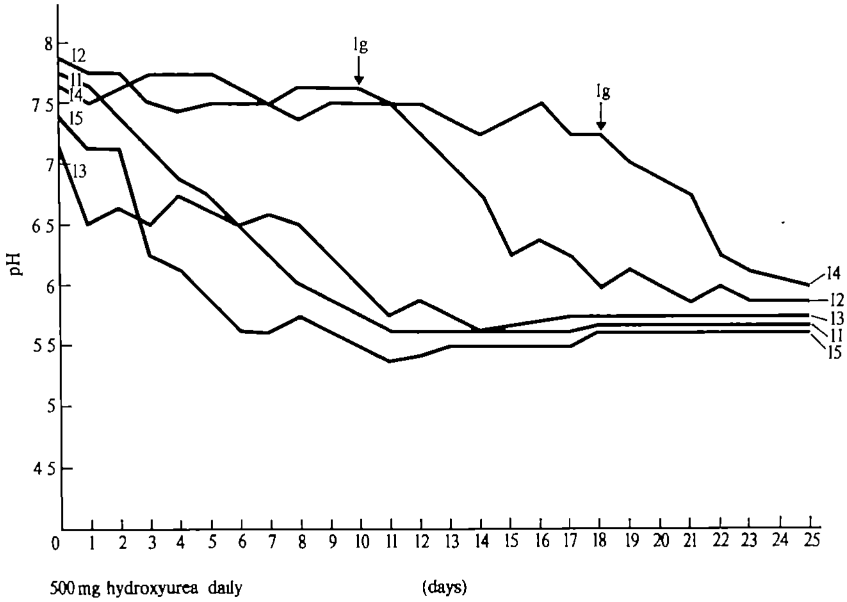

Fig. 3 Mean urinary pH modification during administration of hydroxyurea (patients with renal stones).

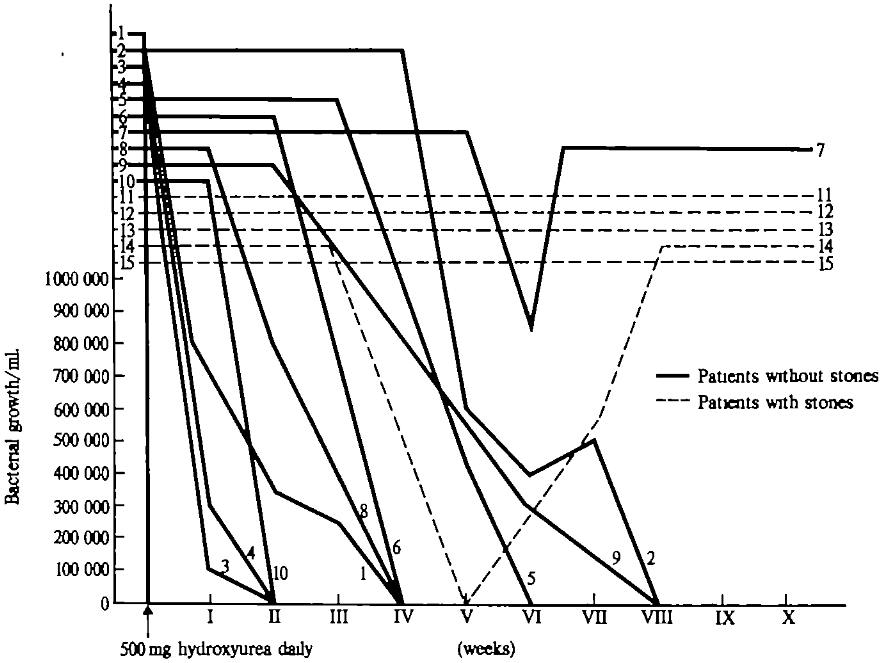

Fig. 4 Urine culture modifications during administration of hydroxyurea.

and no variation has been found. Urinary pH is maintained between 5.8 and 6.8 but so far urine cultures have always been positive for *Proteus* bacteria.

Discussion

On the basis of the work of Griffith *et al.* on hydroxamic acid (Griffith and Musher, 1973; Griffith, 1978a, b; Griffith *et al.*, 1978), the present clinical trial was begun to discover if hydroxyurea is a valid alternative to hydroxamic acid in clinical practice and if it has a place in the clinical management of chronic urinary infection and infective stones.

The results from a small number of cases seem encouraging. Hydroxyurea acidified the urine in all patients, results similar to those obtained by Griffith *et al.* (1978) using hydroxamic acid.

There are 4 different aims that might be reached with the use of urease inhibitors in urological practice:

1. The dissolution of struvite stones when surgery is not possible.
2. The prevention of stone growth in patients with residual calculi due to incomplete surgical removal of staghorn struvite stones.
3. The prevention of new stone formation in patients with previous struvite stones who underwent successful surgical clearance but still suffer chronic urea-splitting urinary infections.
4. The prevention of stone formation in patients with no history of stones but who suffer chronic urease-producing urinary infection.

In all of these cases the aim of treatment is to sterilise and acidify the urine.

It is very difficult to obtain sterilisation of urine in the presence of an infected stone, even if urinary pH is low (Griffith, 1978a; Griffith *et al.*, 1978b; Smith, 1978), because the urine may be reinfected by bacteria trapped within the interstices of the stones.

Our experience with urease inhibitors in stone patients agrees with that of Griffith (1978a), who found in 23 patients that hydroxamic acid did not dissolve stones but seemed to prevent those already there from growing or new ones from forming. Furthermore, we could acidify urine in all of these patients but could not sterilise the urine. The use of hydroxyurea in patients with small residual stones and infection, and in those with persistent infection after surgical removal of staghorn stones or with chronic urea-splitting urinary infections, proved useful. These patients are generally given repeated courses of antibiotics which produce resistant bacterial strains. In our cases, hydroxyurea treatment seemed to act synergistically with antibiotics and to confirm that urinary alkalinity helps bacteria to establish themselves. Urease inhibitors can play an antibacterial role in 2 ways:

1. They inhibit the growth of urea-splitting organisms by acidifying urine.
2. They seem to reduce the nephrotoxic activity of *Proteus* bacteria (Griffith and Musher, 1973; Griffith *et al.*, 1976; Griffith, 1978a, b; Griffith *et al.*, 1978).

In our experience, urine was sterilised in 9 out of 10 patients without stones in between 2 to 8 weeks. Even when urinary sterilisation is not achieved, we think that urine acidification alone justifies treatment with urease inhibitors. The urinary infection alone can account for stone formation because urine becomes supersaturated with struvite and hydroxyapatite only at alkaline pH above 7.3 (Elliot *et al.*, 1958, 1959). We believe that urine acidification must be the main aim in patients with a high risk of struvite stone formation, an aim which cannot be achieved in the presence of urea-splitting organisms by conventional treatment with, for example, ascorbic acid and ammonium chloride. Furthermore, high doses of ascorbic acid may cause hyperoxaluria and ammonium chloride may provoke hypercalciuria by inducing renal acidosis.

Finally, the use of urease inhibitors in clinical practice merits attention because:

1. They produce few side effects.
2. In the form of hydroxyurea they are easily available.
3. They can acidify urine in patients with urinary infection from urea-splitting organisms.
4. They seem to potentiate the effect of antibiotic drugs.

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Case Reports

Predicting Intraperitoneal Bladder Rupture Following Conservative Management of Bladder Contusion

T. G. ALLEN-MERSH, *Department of Orthopaedic Surgery, Charing Cross Hospital (Fulham), Fulham Palace Road, London*

Case Report

A 20-year-old woman car driver was involved in a head-on collision. She was not wearing a seat belt. On admission to the local hospital she was unconscious. She had grazes on the lower abdomen, a fractured right hip but an intact pelvis.

She soon regained consciousness. A Foley catheter was passed into the bladder and bloodstained urine was obtained. During the next 3 days she complained of lower abdominal tenderness. An intravenous urogram (Fig.) showed a bladder dome defect. However, the urinary symptoms settled and the catheter was removed on the fourth day after the accident. The hip fracture was screwed and she went home 2 weeks after the accident, passing urine normally.

A month after the accident, while out shopping, her bladder became uncomfortably full and she experienced sudden lower abdominal pain. Following admission to Yeovil District Hospital, a laparotomy revealed 3 litres of intraperitoneal urine which had escaped from a defect (with overlying plug of omentum) in the bladder dome. This was repaired and she made an uneventful recovery.

Comment

This case is unusual because there was no pelvic fracture or associated perivesical abscess. The bladder rupture followed contusion and was delayed (Turnbull *et al.*, 1978). Thus there was no preceding indication that such a leakage might occur as she had apparently made a complete recovery. However, it might have been predicted had a retrograde stress cystogram (Montie, 1977) been made before the urethral catheter was removed.

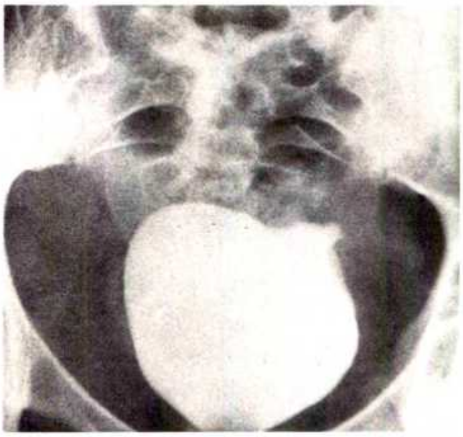

Fig. Cystogram during IVU showing a bladder dome injury which was managed conservatively and which ruptured one month later.

Acknowledgement

I am indebted to Mr P. Knipe, for his permission to report this case.

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Failure of Dissolution of Xanthine Urolithiasis by Local Lavage

R. A. FRAYHA and I. S. SALTI, *Department of Medicine, American University Medical Center, Beirut, Lebanon*

Hereditary xanthinuria (HX), characterised by xanthine oxidase deficiency, hypouricaemia and raised plasma and urinary xanthine and hypoxanthine, has been described in 32 patients (Frayha *et al.*, 1977). The disease is, on the whole, clinically silent, but xanthine nephrolithiasis was described in one-third of the patients. This report describes a new case of HX presenting with obstructive uropathy and severe renal failure. Attempts to dissolve a ureteric xanthine stone by local lavage failed.

Case Report

W.I. had passed several urinary stones since infancy. At the age of 26 years a radiolucent right ureteric stone with a non-functioning right kidney was demonstrated. Serum urate determination and surgery were refused by the patient and he was lost to follow-up for the subsequent 18 years, during which time he passed a number of stones. He was seen by us at the age of 43, when he presented with advanced renal failure. Subsequent studies established the diagnosis of HX (Table). A retrograde pyelogram demonstrated a right ureteric radiolucent stone and pyelonephritic changes in the left kidney. Haemodialysis was started. As an alternative to surgery, 2 attempts were made to dissolve the ureteric stone by local lavage with isotonic sodium bicarbonate via a ureteric catheter but both failed. He underwent a right ureterolithotomy but died post-operatively despite haemodialysis. On chemical analysis the stone was composed primarily of xanthine.

Comment

HX was suggested in our patient when hypouricaemia was present despite advanced uraemia. Xanthine urolithiasis is common in this disease and in some cases the resulting obstructive uropathy necessitated surgical intervention (Frayha *et al.*, 1977). Our patient developed advanced uraemia which was, at least in part, secondary to his basic disease.

Dissolution of uric acid stones utilising local lavage with isotonic sodium bicarbonate has been used as an alternative to operative removal (Nummi, 1973). In our case, failure of 2 such attempts to dissolve the xanthine ureteric stone could be explained, at least in part, by the fact that xanthine is the least soluble of the naturally occurring urinary purines (Seegmiller, 1968).

Acknowledgement

This work was supported by a grant from the Lebanese National Council for Scientific Research.

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Table The Chemical Characteristics of Hereditary Xanthinuria*

	Serum urate µmol/l	*Urinary urate mmol/24 h*	*Plasma oxypurines† µmol/l*	*Urinary oxypurines µmol/24 h*	*Urinary xanthine % of total oxypurines*
Patient W.I.	0	0.05	6.25	1460	60%
Normal range	220-405	1.78-3.57	0.65-1.97	0.20-1.31	

* Methods were previously reported (Frayha *et al.*, 1977).
† Oxypurines denote xanthine plus hypoxanthine.

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Five-Year Survival Following Cystoprostatectomy for Embryonal Rhabdomyosarcoma of the Prostate

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Embryonal rhabdomyosarcoma of the prostate is a rare, highly malignant tumour occurring between the ages of 2 and 6 years and usually presents with urinary retention of rapid onset. Haematuria may be observed and is caused by infection rather than tumour ulceration. Characteristically there is a large, solid, globular mass, which arises from the prostate and which fills the pelvis, displacing the bladder and stretching the urethra (Innes Williams, 1968).

Case Report

A boy, aged 3 years 10 months, was admitted with a distended bladder and a 2-month history of recurrent bouts of retention and haematuria. After decompression of his bladder no abdominal mass could be felt. His urine contained red cells and was infected with *Staph. aureus*. An intravenous urogram showed a filling defect at the bladder neck, without obstruction to the upper urinary tract (Fig.).

Cystoscopy revealed a nodular lesion in the posterior urethra and on rectal examination there was a 3 cm prostatic mass. A biopsy of this lesion was taken through the resectoscope and reported as embryonal rhabdomyosarcoma of the prostate showing characteristic striations. An ileal conduit was fashioned and 4 weeks later a total cystoprostatectomy performed.

Two years later he developed a further bout of urethral bleeding, but no recurrence was detected on urethroscopy. It is now 5½ years since operation and he is alive and well without evidence of tumour.

Comment

This is the first reported case of prostatic rhabdomyosarcoma, treated by surgery alone which has survived more than 5 years. In some respects this case was atypical, the tumour being smaller, the symptoms less acute and the rate of growth slower than usual. The success of treatment may be attributed to the relatively benign biological character of the tumour. Of recent years adjuvant chemotherapy has been employed in the treatment of rhabdomyosarcoma of the urinary tract. Goodwin *et al.* (1968) reported an example of 5-year survival following combined surgery and chemotherapy.

Although operation was performed in 2 stages, cystectomy proved to be easy and it was felt afterwards that the 2 operations could have been combined.

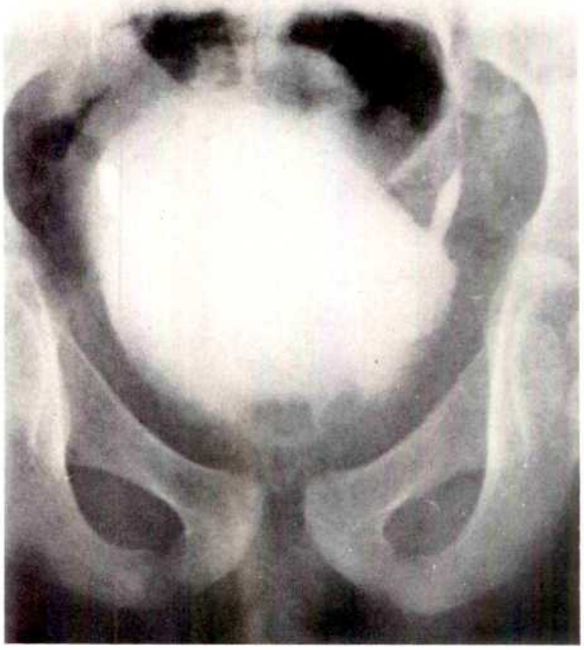

Fig. Bladder film from IVU series showing filling defect at the bladder neck.

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Relief of Malignant Ascites due to Disseminated Carcinoma of the Kidney, using the LeVeen Shunt

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C. M. EVANS, *The Royal Liverpool Teaching Hospital*

The treatment of ascites by peritoneovenous shunting, using a specially designed one-way pressure activated valve, was described by LeVeen *et al.*, in 1974. Most of the early cases treated in this way were cirrhotics, but a few had malignant disease. Although survival may not be prolonged, morbidity is reduced and renal function often improves because the hepatorenal syndrome is relieved and diuretics are no longer required (Wapnick *et al.*, 1977).

Case Report

The patient was a 48-year-old male. At the age of 44 he had a myocardial infarct and was anticoagulated with warfarin. Eighteen months before the diagnosis of renal carcinoma was made he presented with haematuria which was ascribed to anticoagulants. A right nephrectomy was carried out. The renal vein contained tumour but a chest X-ray was clear. After a short convalescence the renal bed was irradiated.

Three months later the patient presented with jaundice and ascites (alk. phosphatase 1215 iu/l, Gamma GTP 545 iu/l, bilirubin 30 μmol/l). He was treated with medroxyprogesterone, frusemide and spironolactone, and paracentesis was carried out at 3-monthly intervals. Despite these measures he continued to deteriorate and his renal function began to fail (urea 9 mmol/l).

Eight months after nephrectomy the valve (Becton-Dickinson and Co.) was inserted subcutaneously and a fenestrated tube drained the peritoneal cavity through the valve into the internal jugular vein via a subcutaneously tunnelled silicone tube. He was discharged on the fifth post-operative day after an uneventful recovery. His weight and girth fell progressively and finally stabilised. He was taught to monitor each himself. Despite his infarct, circulatory problems were not experienced and he did not require diuretics but continued to take medroxyprogesterone.

He remained stable over the following month and his renal function returned to normal. However, after a violent sneeze he suddenly developed abdominal pain and his girth and weight progressively increased. At operation the peritoneal fenestrated tube was freed of omentum and again he made an uneventful recovery.

Three months later the valve ulcerated through the skin and a skin flap was made to bury it, but it functioned unimpaired.

It is now 38 months since the valve was inserted, and the patient is alive and has returned to work. His renal function has remained normal and although his liver function tests remain abnormal, they have improved considerably (alk. phosphatase 572 iu/l, Gamma GTP 400 iu/l, bilirubin 10 μmol/l).

Comment

Advanced carcinoma with ascites is as distressing for the patient as it is difficult to treat. Diuretics are of limited value and may cause metabolic problems which lead to renal failure. Paracentesis distresses the patient and may cause protein depletion, renal failure and even sudden death. The LeVeen valve allows the continuous infusion of ascitic fluid, which can be beneficial (Vlahcevic *et al.*, 1967) and is more successful than previous designs.

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Ureteric Trauma by Catheterisation of Tuberculous Bladders

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Rare but dangerous ureteric trauma by catheterisation of a tuberculous bladder occurred twice in our department.

Case 1. A Foley catheter was introduced into the tuberculous bladder of a 78-year-old woman to avoid frequent micturition due to a reduced bladder capacity. After the catheter was replaced 10 days later the patient developed severe colic in the right flank. The Foley catheter had been placed into the right ureter and periureteric extravasation could be seen on excretion urography (Fig. a). The introduction of a ureteric catheter at cystoscopy was impossible as the ureteric orifice was not seen. However, a small Foley catheter could be placed without difficulty in the right renal pelvis and this allowed healing of the ureter (Fig. b). After removal of the Foley catheter ureteric healing was confirmed (Fig. c).

Case 2. V.D.B. was a patient with advanced urinary tuberculosis and small bladder capacity. He refused a urinary diversion and was treated with an indwelling catheter.

Once, while changing his Foley catheter he complained of severe pain in the right flank. Urography showed the Foley catheter to be localised in the ureter but fortunately the balloon was not inflated and ureteric injury was prevented. Subsequently, whenever the catheter was pushed too far, the patient would never omit to tell us that the catheter should be redrawn.

Comment

When the bladder has a reduced capacity, as in urinary tuberculosis, the ureterovesical junctions lie close to the internal meatus of the urethra. If, in addition, the ureters are dilated, the introduction of a bladder catheter should be done with great care as catheterisation of the ureter can occur.

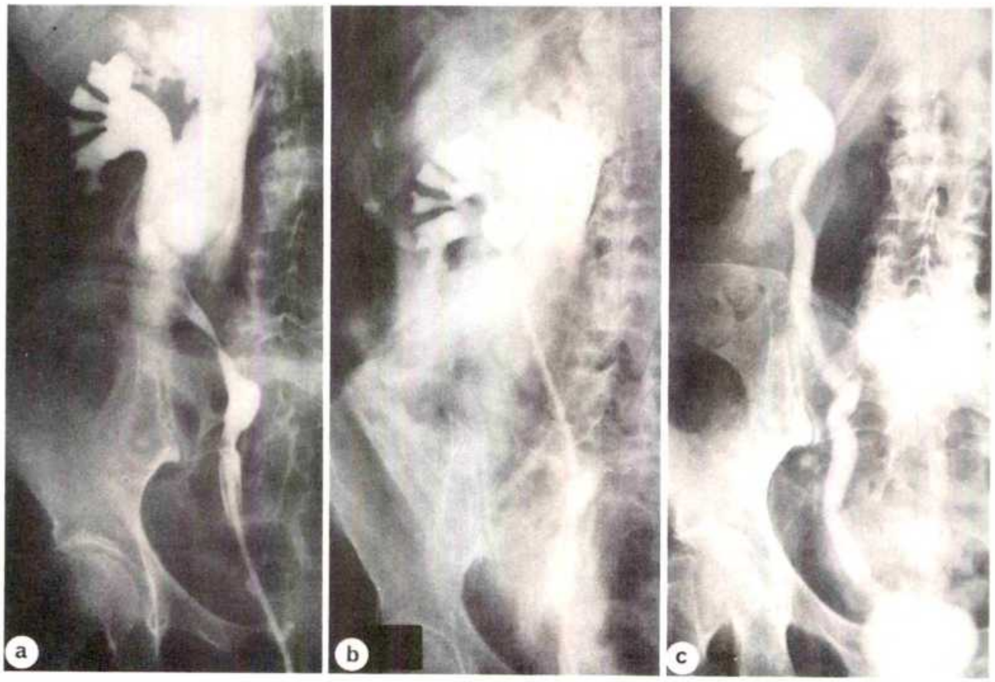

Fig.

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Pseudotumour of the Bladder Associated with Outflow Obstruction

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Case Report

A man aged 74 was admitted with a 2-year history of prostatic symptoms culminating in acute retention of urine. After catheterisation and decompression of the bladder a firm, non-tender, suprapubic mass was palpable. Bimanual examination revealed a benign 50 g prostate and a firm mass about 8 cm in diameter arising from the fundus of the bladder. Intravenous urography showed back pressure changes in the upper urinary tract but no gross distortion of the bladder outline. At cystoscopy the mucosa of the bladder fundus was replaced by a papilliferous mass, which was biopsied. The biopsies showed inflammatory and hyperplastic changes only, so open exploration was carried out to exclude a bladder carcinoma. At operation a smooth, firm mass 3 cm thick was found arising from the fundus of the bladder which was otherwise normal. A full thickness biopsy was taken and again revealed only hyperplasia and inflammation (Fig.). The patient was therefore sent home with an indwelling urethral catheter and at out-patient follow-up one month later the mass had disappeared. He was readmitted for transurethral prostatectomy. Following this he recovered uneventfully and the mass did not recur.

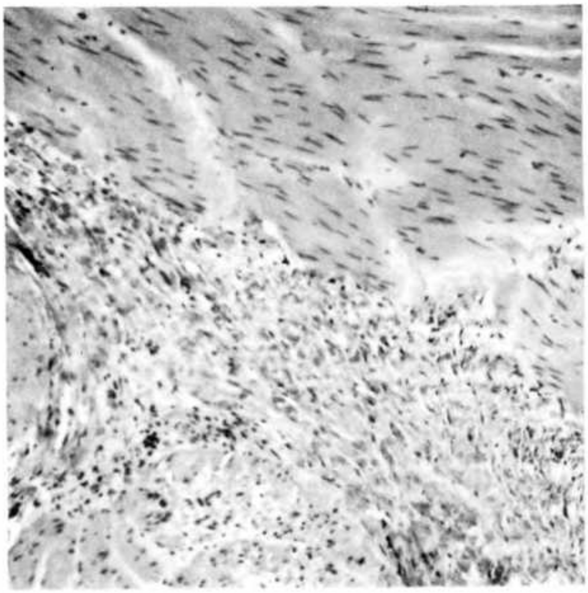

Fig. Section taken from bladder fundus, showing muscular hyperplasia and non-specific inflammatory changes (×400).

Comment

The papilliferous and hypertrophic changes which may occur in the bladder mucosa as a result of inflammation were described in detail by Marion and Hertz-Boyer (1923). Several inflammatory conditions may thus simulate the cystoscopic and radiological appearances of bladder carcinoma; recent reports have emphasised the difficulty of making this distinction (Goldstein *et al.*, 1971; Berman and Wilets, 1977). Biopsy is essential although even this may be misleading (Lamm and Gittes, 1976).

The occurrence of a palpable tumour of the bladder wall caused by outflow obstruction has not been reported previously. Presumably this was a manifestation of cystitis directly related to the bladder neck obstruction. A wider awareness of the entity of bladder pseudotumour may in some cases allow a more conservative approach to treatment and prevent unnecessary surgery.

Acknowledgement

I thank Mr A. P. J. Ross for permission to present a patient under his care.

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Vaginal Metastasis of Renal Carcinoma Without Renal Vein Involvement

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Vaginal metastasis from a renal carcinoma is rare. Fifty-five cases are reported in the world literature (Redman and Roman-Lopez, 1977). A patient with a renal carcinoma who presented with vaginal bleeding is reported.

Case Report

A 64-year-old white woman was admitted for evaluation of post-menopausal bleeding. She had a 5-month history of fullness and pain in the left upper quadrant. Physical examination revealed an 8 cm, hard, non-tender, left upper quadrant mass. Pelvic examination demonstrated bleeding from a 2 × 3 cm, exophytic, friable mass on the left lateral vaginal wall. Urine analysis showed 5 to 10 red blood cells per field. An excretory urogram demonstrated a space-occupying lesion of the lower pole of the left kidney. Renal arteriography confirmed a left renal carcinoma with a patent renal vein (Fig.).

Following successful embolisation of the renal tumour, the patient underwent a radical left nephrectomy and excision of the vaginal lesion. The kidney demonstrated a renal carcinoma with capsular and pericapsular invasion. The main renal vein and renal pelvis were free of tumour. The vaginal lesion was consistent with a metastatic renal carcinoma.

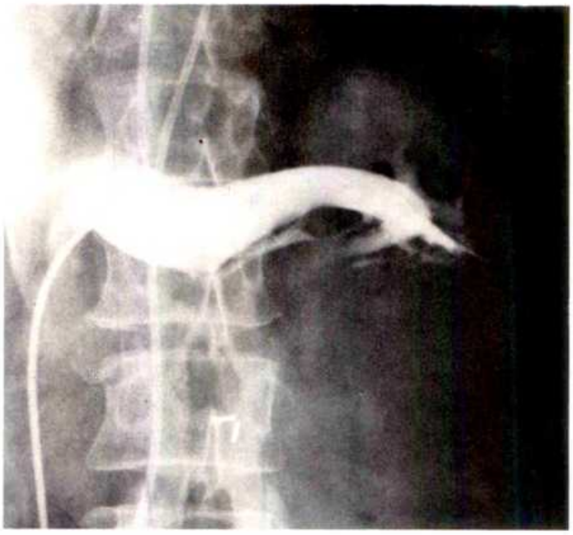

Fig. Renal arteriography. Venous phase reveals a patent left renal vein.

Comment

Migration of tumour cells to the vaginal wall via the urinary tract, renal vein and systemic circulation, and retrograde lymphatic system seems improbable (Mulcahy and Furlow, 1970). The predilection of the primary tumour to the left kidney favours the hypothesis of retrograde embolism down the left ovarian vein to the pampiniform and uterovaginal plexuses. This event is more readily conceived to follow occlusive tumour invasion of the left renal vein with permanent reversal of venous flow and embolic tumour fragments detached and carried caudally. Radiographic evidence of retrograde filling of the left ovarian vein and left ovarian and vaginal plexuses in a patient with tumour involvement of the renal vein has been shown (Mulcahy and Furlow, 1970).

Retropulsion of tumour embolism in cases with unobstructed main veins secondary to sudden increases in intrathoracic and intra-abdominal pressure has remained unconvincing and proof has been lacking (Willis, 1973). However, this case with radiological and pathological absence of renal vein involvement may be an example of this phenomenon.

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Author's Follow-up

Aminoglutethimide: Medical Adrenalectomy in the Management of Carcinoma of the Prostate. A Review after 6 Years

M. R. G. ROBINSON, *Department of Urology, Pontefract General Infirmary, Southgate, Pontefract, West Yorkshire*

Aminoglutethimide blocks the conversion of cholesterol to delta 5-pregnenolone in the adrenal gland and therefore inhibits the production of aldosterone, cortisol and androgens (Cash *et al.*, 1967). There is no evidence that it influences the production of testosterone by the testes (Gaunt *et al.*, 1968). In 1970 at the Institute of Urology, London, selected patients with advanced prostatic cancer were treated with aminoglutethimide to determine the effect of suppression of their adrenal androgens ("medical adrenalectomy"). The results were published by Robinson *et al.* in 1974 and this paper reviews that study 10 years after it began.

Twenty-six patients were given aminoglutethimide 500 to 1000 mg daily in divided doses and stilboestrol 1 mg 3 times a day. They also received cortisone 20 to 25 mg daily and fludrocortisone 0.1 mg daily. Four patients were not given steroid replacement therapy for one to 2 weeks after commencing aminoglutethimide and 3 of these became hypertensive, with clinical evidence of acute adrenal failure. Subjectively, 8 patients (30%) had complete relief of pain from metastases and 9 (35%) had partial relief of symptoms. Objectively, these patients were not assessed by criteria which would currently be acceptable. However, 13 patients had elevated acid phosphatase levels and during therapy these levels fell to normal in 4 (31%). One patient, with a normal acid phosphatase, demonstrated decreased activity of bone metastases on repeated scintigraphy and one showed a marked reduction of prostatic size on rectal examination. Another patient demonstrated resolution of ureteric obstruction on intravenous urography. In this original series we were unable to measure a fall in plasma cortisol levels in 4 patients who received aminoglutethimide before steroid replacement. In addition, none of the patients who were receiving stilboestrol 1 mg 3 times a day demonstrated a further fall in plasma testosterone levels as measured by the method described by Shearer *et al.* (1973). These observations were almost certainly a reflection of laboratory method. More recent studies of aminoglutethimide in the management of breast cancer have demonstrated a marked fall in plasma and urinary steroids including cortisol (Newsome *et al.*, 1977; Harvey *et al.*, 1979) and in a previous study (Robinson and Thomas, 1971), using a different laboratory method, we were able to demonstrate a fall in plasma testosterone during the aminoglutethimide therapy in patients on stilboestrol.

In our original paper we concluded that aminoglutethimide had only a limited role in the palliation of oestrogen-resistant carcinoma of the prostate, even though we were able to report a good subjective response in 8 patients and some evidence suggestive of objective response in 7. This cautious opinion was based on the incidence of side effects experienced by our patients. These included hypotension, nausea and vomiting, lassitude, depression, oedema and skin rashes. More recently, Sanford *et al.* (1976) have reported a favourable response to aminoglutethimide therapy in 3 of 7 patients with progressive stage D prostatic carcinoma. Their criteria of response were based on radiological evidence of regression of bone metastasis (1 patient) and a fall in acid phosphatase levels (2 patients). Several reports have shown a response of metastatic breast cancer to aminoglutethimide with acceptable side effects (Koelmeyer *et al.*, 1978; Wells *et al.*, 1978; Harvey *et al.*, 1979). At the present time the side effects of aminoglutethimide do not appear excessive when compared to those due to the cytotoxic chemotherapy so often used in advanced malignant disease. It seems imperative that a properly designed phase II trial, using acceptable criteria of objective response, should be done to reassess the value of aminoglutethimide in the management of advanced prostatic cancer.

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Conferences and Courses

Manchester and North West Region Kidney Research Association. One-Day International Symposium on Idiopathic Hydronephrosis

Manchester. 5 September 1980.

Registration fee £15.00. Further particulars from: P. H. O'Reilly, Department of Urology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Edinburgh Urological Festival

Edinburgh. 1-3 September 1980.

A postgraduate course in urology for consultants, senior registrars and registrars. The topics to be covered include: unstable bladder, urethral syndrome, prostatitis, equivocal obstruction, upper and lower tract tumours, investigative techniques, calculi.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG, Scotland.

Second Meeting of the International Society for Dynamics of the Upper Urinary Tract (ISDU)

Stanford, USA. 7-8 October 1980.

For information on the meeting please contact: C. E. Constantinou, Assistant Professor of Surgery (Urology), Stanford University Medical Center, Stanford, California 94305, USA.

For information on membership of ISDU please contact: B. Coolsaet, Professor of Urology, Academic Hospital, Utrecht, The Netherlands.

Swiss Society of Urology: 36th Annual Meeting

Montreux, Switzerland. 16-18 October 1980.

Further particulars from: Prof. K. Bandhauer, Secrétaire de la SSU, Clinique urologique, Hôpital cantonal, CH-9007 St-Gallen.

Nordic Association for Andrology. Early Diagnosis of Testicular Cancer

Copenhagen, Denmark. 5-7 November 1980

A workshop and symposium dealing with testicular carcinoma *in situ*, epidemiology, clinical aspects of testicular tumours and the early diagnosis cancer. Papers will be presented by an international panel of experts.

Further particulars from: Dr N. E. Skakkebaek, Laboratory of Reproductive Biology, 4052 Rigshospitalet, Blegdamsvej 9, DK 2100, Copenhagen Ø, Denmark.

Institute of Urology (The University of London)

Preliminary announcement of seminars to be held Autumn 1980 to Summer 1981

October 1980: Treatment of the unstable bladder—1 day seminar.
The renal papilla—1 day seminar.
Diagnosis and treatment of erectile impotence—1 day seminar.
Urological oncology—2 day seminar.

November 1980: Advances in renal transplantation—1 day seminar
Radioisotopes in urology and nephrology—1 day seminar.
Upper tract endoscopy—1 day seminar.

December 1980: Renal homeostasis—1 day seminar.
Uro-Radiology weekend—2 day seminar.

January to March 1981: The Scientific Basis of Urological Practice—10 week course.

April or May 1981: Endoscopic surgery—3 day seminar.

July 1981: Testicular tumours and tumour markers—2 day seminar.

For details apply to: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01-836 5361.

Institute of Urology (The University of London) Ten Week Course on The Scientific Basis of Urological Practice

12 January-20 March 1981

A full-time non-residential course covering all aspects of urological practice undertaken at the Institute and its associated St Peter's Hospitals.

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For further details and application form contact: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01-836 5361.

First Meeting. Urological Days of Necker

Paris, France. 12-14 March 1981.

The topics are:

(1) Tumours of calices, renal pelvis and ureter.
(2) Ureteropelvic junction obstructive anomalies.

The mornings of 12 and 13 March will be devoted to televised operations. The afternoons of these 2 days and the morning of 14 March will be devoted to communications. Each speaker will have 30 minutes at his disposal and the lectures will be published as monographs by Masson.

Further information from: Secrétariat des Journées Urologiques de Necker, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

Second Congress of the International Society of Urologic Endoscopy

Bristol. 9-11 September 1981.

Those wishing to join the Society should contact the Honorary Secretary, Dr Jorge Morera, Federico Lacroze 2154, (1426) Buenos Aires, Argentina.

Those interested in attending the meeting should contact Miss Sarah Storie-Pugh, Conference Services Ltd, 3 Bute Street, London SW7 3EY.

Book Reviews

Ultrasound in Urology. Edited by M. I. Resnick and R. C. Sanders. Pp. xv + 390. Baltimore: Williams and Wilkins, 1979. Price $45.00.

To the best of my knowledge this is the first ultrasound text to be published which is devoted exclusively to the current place of this imaging modality in urological practice, and it is interesting to see a clinical urologist sharing the editorial responsibility with one of this country's better known ultrasonic experts whose experience in the field is extensive and whose writings are both prolific and sometimes controversial. One would expect from such a combination a comprehensive yet practical approach to the subject and in most respects this has been more than adequately achieved.

The introductory chapters covering historical aspects, physics and instrumentation have, I suspect, been kept intentionally brief in order to cover only the broad principles fundamental to the understanding of the subject. The reader is then orientated by chapters on cross-sectional and ultrasonic anatomy. These correlate reasonably well, but it is irritating to see anatomists once again deferring to the sacred cow of CT and showing their sections in the coronal plane only, seemingly unaware that ultrasound can offer not only sagittal sections but almost any other orientation too.

An excellent short chapter on the adrenal glands is followed by the meat of the book, comprising sections on cystic disease, tumours, trauma and retroperitoneal problems. Ultrasound of the lower urinary tract is followed by an interesting chapter on testicular pathology. The paediatric urinary tract and renal transplantation are adequately covered. The final chapters deal with various ultrasonically assisted procedures and include discussion of its role in radiotherapy and even bladder stone destruction.

The 400 pages of this book provide a broad working knowledge of what ultrasound can offer the urologist and it is gratifying to see how often the modality is related to clinical problems. The bibliography is as up

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to date as can be expected in such a rapidly expanding field. Although there is an abundance of photographs, quality is often mediocre and many are difficult to interpret, particularly as in the United Kingdom we are used to viewing the white on black format (which undoubtedly reproduces better illustrations and slides). Perhaps the disappointing pictures reflect to a certain extent the unparalleled advances in technology and improved image quality to which we have become accustomed in the last 2 years.

With a few reservations, then, we have here a good standard text which will undoubtedly help the urologist to see and understand what the ultrasonographer has hitherto asked him to believe. The price of $45.00 is not unreasonable by today's standards.

A.U.A. Courses in Urology. Edited by W. W. Bonney, W. L. Weems and J. P. Donohue. Volume 1. Pp. xii + 288. Baltimore: Williams and Wilkins, 1979. Price £15.50, $23.10.

The wide range of activities of the American Urological Association in postgraduate education is well known and this book is a natural development from their seminars and courses. Volume 1 contains 3 symposia covering the subject of urethral stricture, neurogenic bladder and voiding problems in children. In addition there are 7 chapters on various other topics including anatrophic nephrolithotomy and pelvic lymphadenectomy. The style is direct and informative and while experts in any of these topics might well feel a lack of balance in some of the presentations and opinions, there can be no doubt about the views of the authors. This book is good value for money.

Acid-Base and Potassium Homeostasis. Edited by Barry M. Brenner and Jay H. Stein. Pp. 300. Edinburgh: Churchill Livingstone, 1979. Price £15.00.

This second volume in *Contemporary Issues in Nephrology* is a scholarly and interesting book for all who are interested in the problems posed by acid-base balance and potassium homeostasis. The initial chapters form a physiological review of hydrogen ion and potassium handling by the kidney and the disorders underlying the acidoses of renal origin.

Although recent research has added a great deal of controversy, the chapter on Bartter's syndrome still presents an excellent review of this rare but fascinating disease. Illustrations are few, but clear, and the references provided at the end of each chapter are well selected. This book would be of particular value to junior staff who wish to grasp the fundamentals of these subjects, together with their clinical application, in an eminently readable form.

Renal Calculus. Leslie N. Pyrah. Pp. xiv + 370. Berlin: Springer-Verlag, 1979. Price $49.00 (DM 89.00).

This book is the compilation of a life-time of surgical and experimental work on urinary tract stone disease. Its particular strength lies in the uniformity of style and depth of knowledge. It would certainly be unwise to report a "new" stone operation or "new" biochemical finding without first consulting this volume. A useful addition to all urological and renal departmental libraries.

Urinary Calculous Disease. Edited by J. E. A. Wickham. Pp. 207. Edinburgh: Churchill Livingstone, 1979. Price £11.00.

This is an excitingly presented, well referenced book. Each section is written by an acknowledged expert; this does lead to some lack of uniformity and possibly some theories are advanced which may later be refuted. However, this book conveys up-to-date thoughts on stone genesis and treatment with comprehensive lists of references. Those surgeons who still find that staghorn calculi recur after operative removal would do well to consult the chapter on surgical treatment. This book is highly recommended.

Proceedings of the European Dialysis and Transplant Association. Edited by B. H. B. Robinson, J. B. Hawkins and R. B. Naik. Volume 16. Pp. xix + 785. Tunbridge Wells: Pitman Medical, 1979. Price £25.00.

The editors and the publishers of these Proceedings must be congratulated on producing this book within 9 months of the EDTA meeting in Amsterdam in 1979. Once again this book provides a valuable source of statistics on the subject in addition to the many papers giving up-to-date information and commentary on dialysis and transplantation.

Books Received

Renal Medicine. E. N. Wardle. Guidelines in Medicine, Volume 2. Pp. vii + 435. Lancaster: MTP Press Ltd, 1979. Price £15.95.

Urologie Clinique. Jean Cibert, Jacques Cibert, André Gilloz and Reza Massoumi. Pp. 347. Paris: Masson, 1979.

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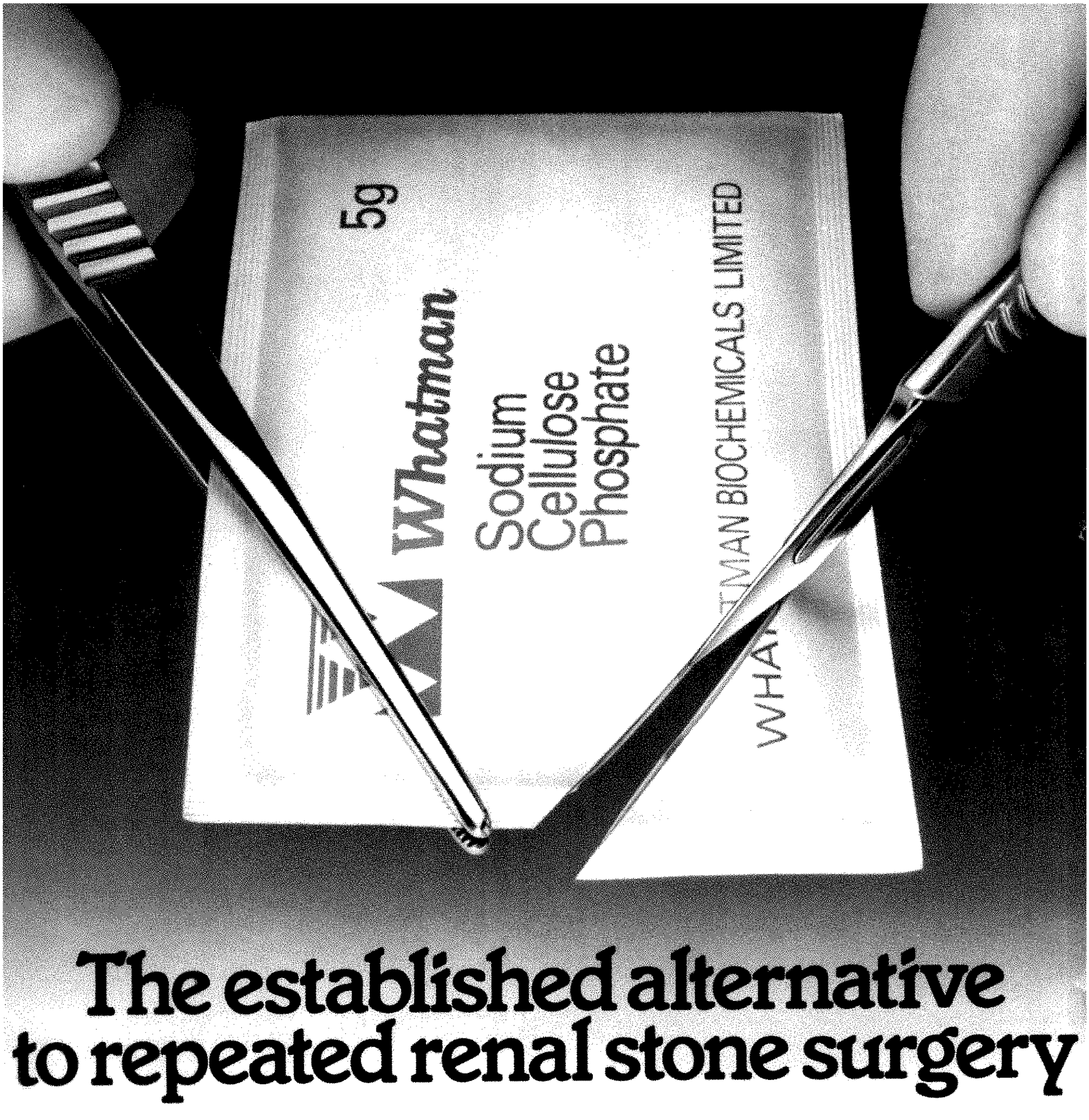

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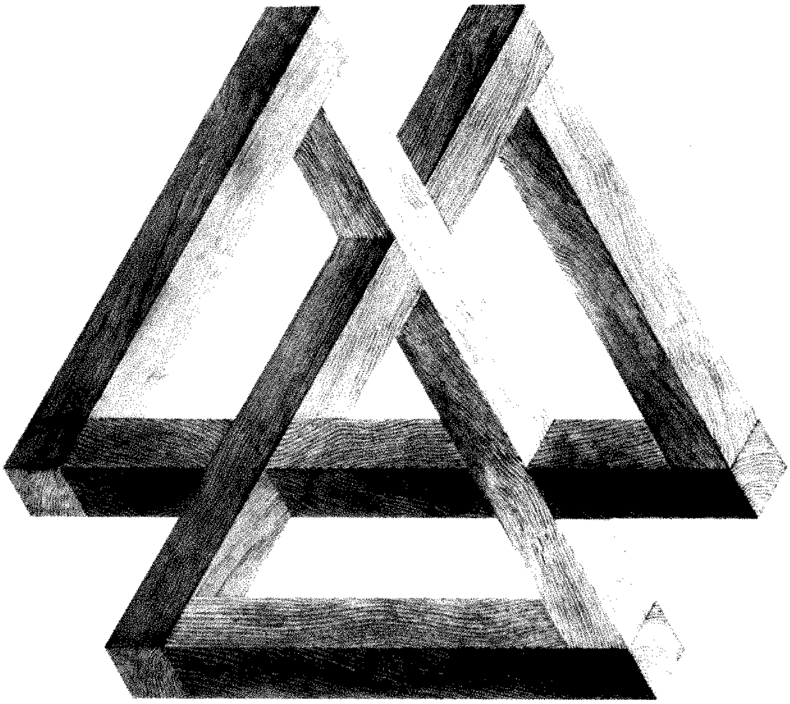

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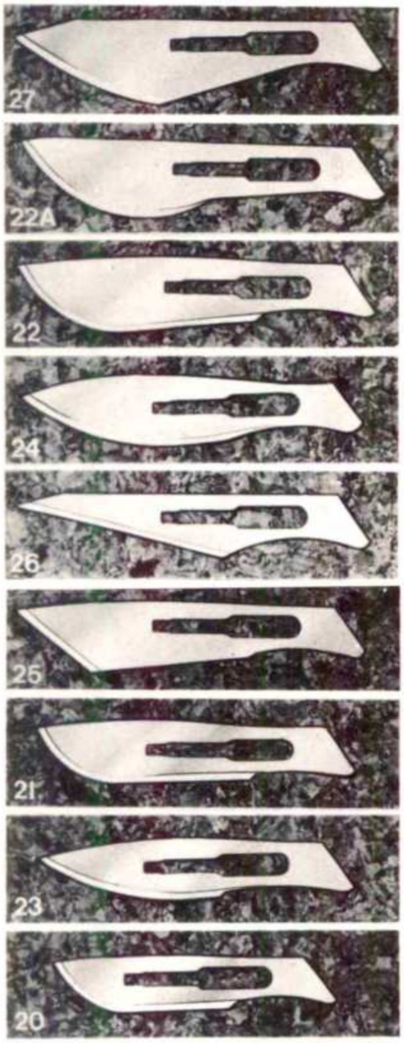

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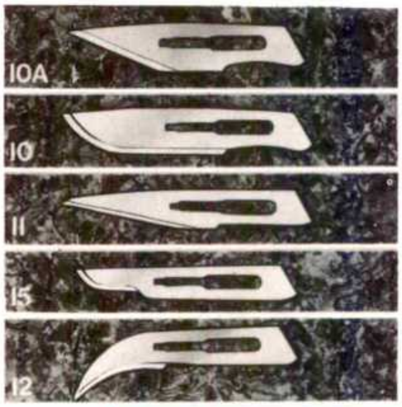

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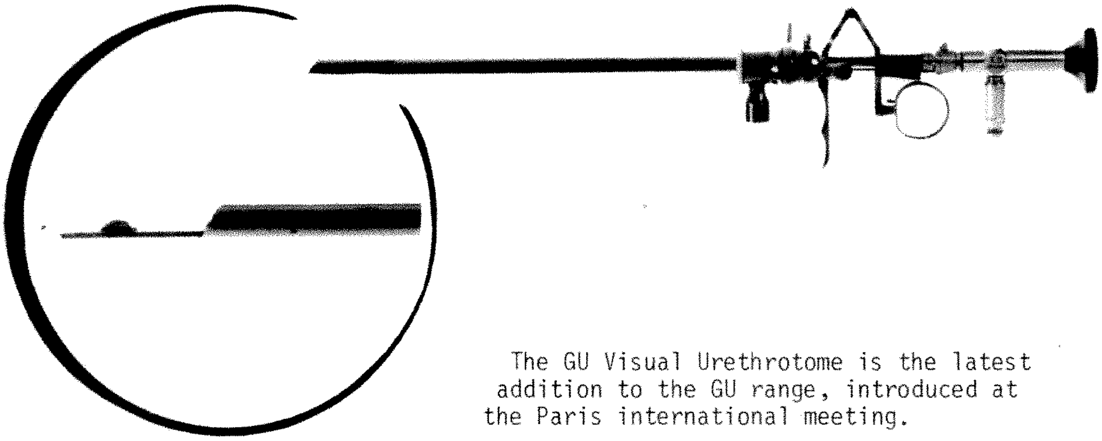

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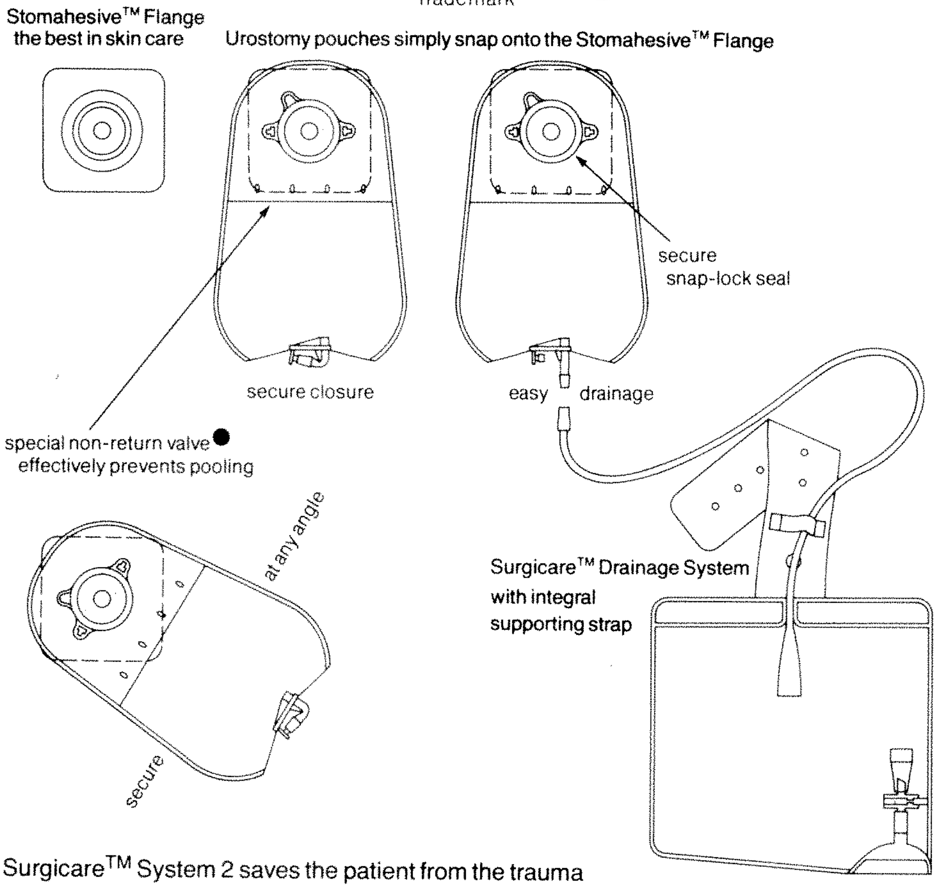
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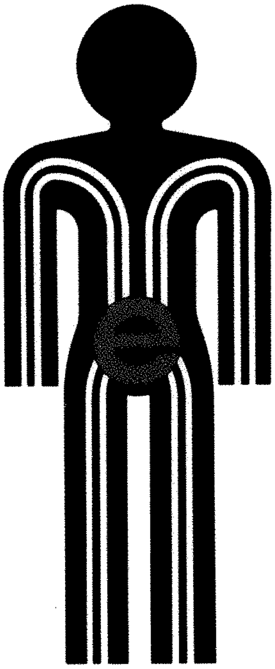

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Adverse Reactions. Commonly transient nausea, occasionally vomiting and rarely diarrhoea, gynaecomastia, angina, rash and/or fever, transient disturbance of liver function.
Contraindications. Peptic ulceration, severe liver disease or severe cardiac disease. Children.
Pharmaceutical Precautions. Store in cold place (2°C to 8°C).
Package Quantities. Bottles of 100 capsules.
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References
1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer, E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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sulphate equivalent to
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contains methyl and propyl
ıben. AMIKIN PAEDIATRIC
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nikacin activity 100mg. The
ampoule contains no
reservatives. **Uses** AMIKIN
nikacin sulphate) is a semi-
synthetic aminoglycoside
antibiotic which is active
gainst a broad spectrum of
Gram-negative organisms,
ıcluding Pseudomonas and
some Gram-positive
organisms.
Dosage and Administration
*ramuscular or intravenous
administration* For most
ıfections the intramuscular
ute is preferred, but in life-
hreatening infections, or in
patients in whom
ramuscular injection is not
feasible, the intravenous
route, either slow bolus
(2-3 minutes) or infusion
(30 minutes) may be used.
lts and children 15mg/kg/
day in two equally divided
ses. Use of the 100mg/2ml
rength is recommended for
children for the accurate
measurement of the
ppropriate dose. *Neonates
and premature infants* An
al loading dose of 10mg/kg
ved by 15mg/kg/day in two
equally divided doses. *Life
eatening infections and/or
e caused by pseudomonas*
. The adult dose may be
ased to 500mg every eight
hours but should neither
exceed 1.5g/day or be
administered for a period
longer than 10 days. A
aximum total adult dose of
5g should not be exceeded.
Impaired renal function In
atients with impaired renal
ction, the daily dose should
duced and/or the intervals
etween doses increased to
accumulation of the drug.
*tra-indications, warnings,
tc* Patients should be well
hydrated during AMIKIN
therapy. In patients with
impaired renal function or
diminished glomerular
tration, AMIKIN should be
used cautiously. In such
ents, renal function should
be assessed by the usual
thods prior to therapy and
odically during therapy. As
ith other aminoglycosides,
ototoxicity and/or
hrotoxicity can result from
se of AMIKIN; precautions
on dosage and adequate
ation should be observed.
use of AMIKIN in patients
with a history of allergy to
oglycosides or in patients
may have subclinical renal
or eighth nerve damage
ed by prior administration
ephrotoxic and/or ototoxic
ents should be considered
caution, as toxicity may be
additive. In these patients
MIKIN should be used only
if, in the opinion of the
physician, therapeutic
advantages outweigh the
potential risks. The risk of
toxicity is increased when
KIN is used in conjunction
vith rapidly acting diuretic
ugs, particularly when the
diuretic is administered
ıtravenously. Such agents
include frusemide and
crynic acid, which is itself
totoxic agent. Irreversible
deafness may result.
Pregnancy: The safety of
KIN in pregnancy has not
et been established. **Side
effects**: When the
mended precautions and
dosages are followed the
idence of toxic reactions,
h as tinnitus, vertigo, and
partial reversible or
rreversible deafness, skin
sh, drug fever, headache,
paraesthesia, nausea and
is low. Urinary signs of
irritation (albumin, casts,
and red or white cells),
taemia and oliguria have
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er antibacterial agents in
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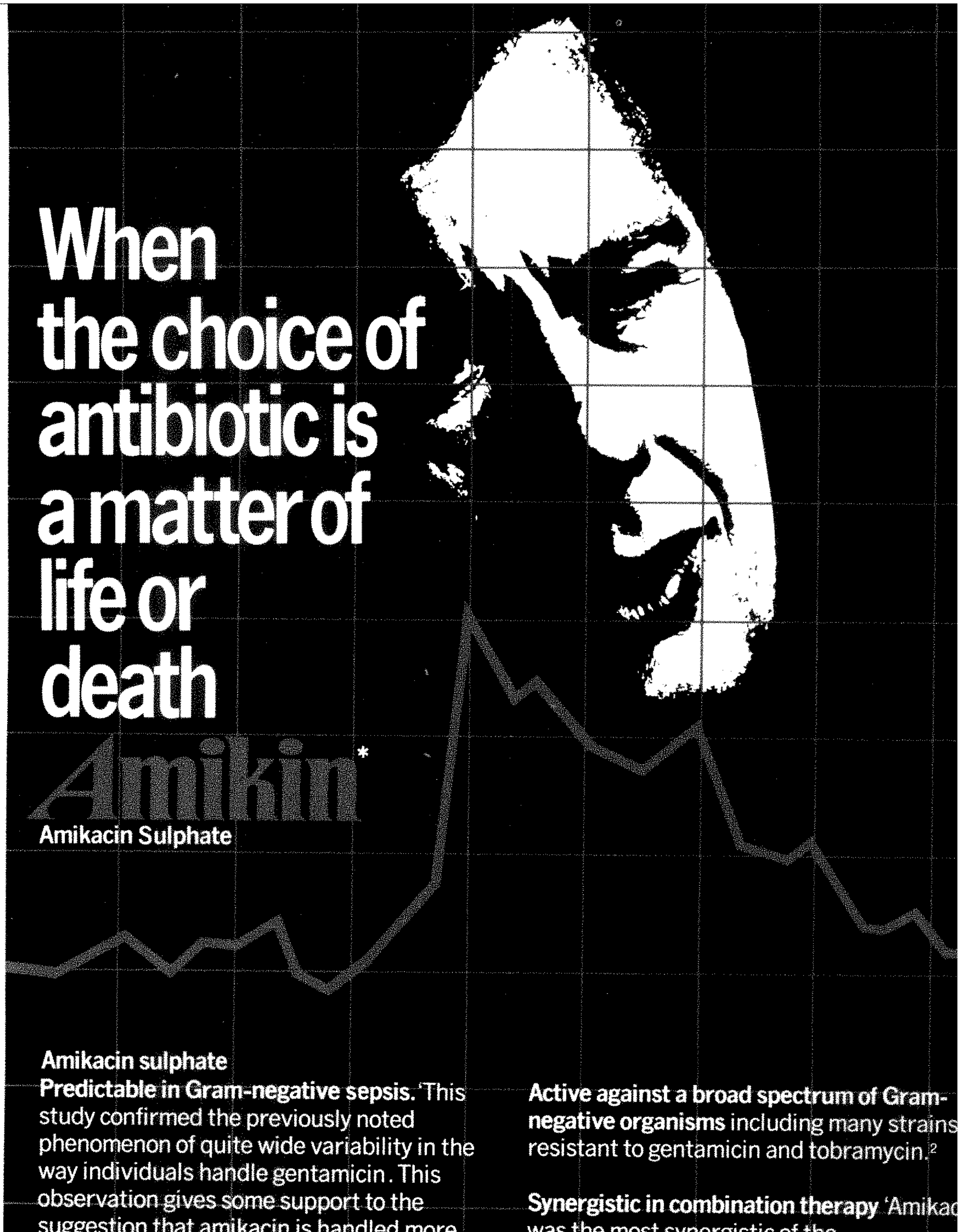

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2. Reynolds AV, *et al.*, *Brit. Med. J.*

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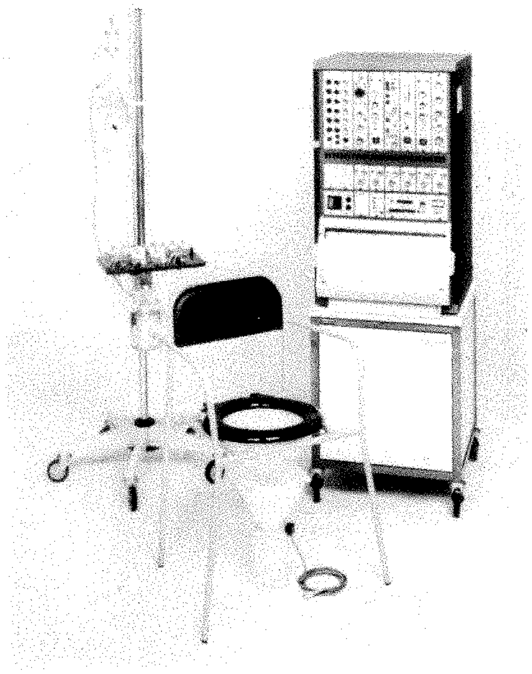

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Antibiotic	No. of Patients	% Side Effects
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Co-trimoxazole	83	21
Trimethoprim	**84**	**8**
Total	339	

Prescribing information

IPRAL tablets
Each tablet contains trimethoprim B.P. 100 mg.

Indications
Ipral is indicated for the treatment and prophylaxis of acute and chronic urinary tract infections.

Actions
Ipral is active in-vitro against most pathogenic Gram-positive and Gram-negative bacteria. Exceptions include Neisseria species and Pseudomonas aeruginosa.

Dosage and administration
For acute urinary tract infections 2 tablets twice daily is recommended
For long term and prophylactic therapy 1 tablet twice daily is recommended.

Contra-indications
Ipral should not be given to patients with severe renal insufficiency where blood levels cannot be monitored regularly. Ipral should not be used in pregnancy or during the first few weeks of life

Precautions
Care is necessary in administration to patients with impaired renal function. Special precaution should be exercised in patients with a predisposition to folate deficiency.

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Nausea, vomiting and skin rashes may occur but are rare. Ipral may depress haematopoiesis during prolonged therapy. This has proved reversible when treated with calcium folinate.

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References
1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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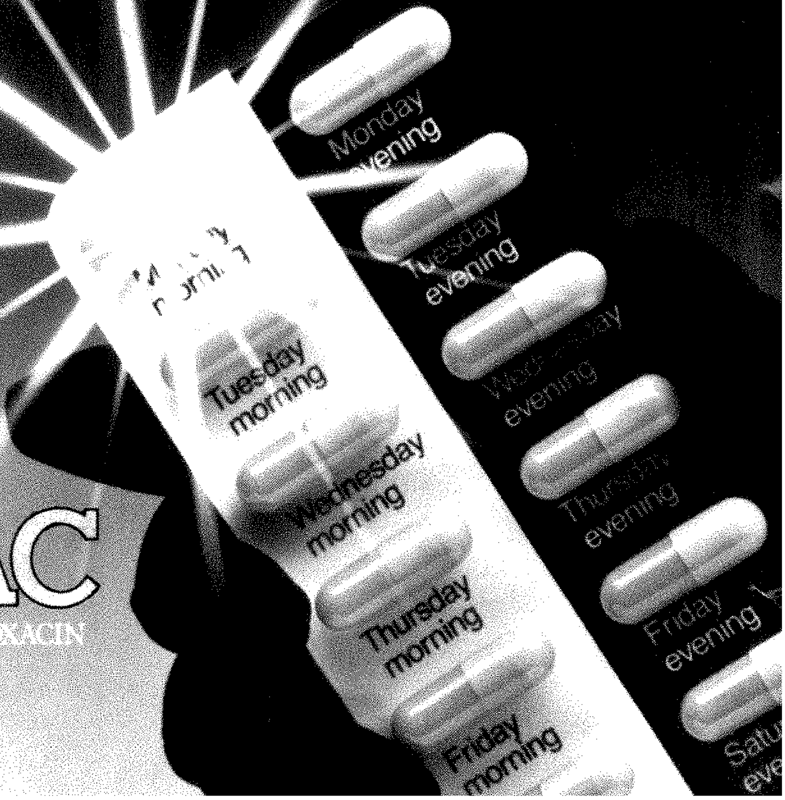

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"CINOBAC" Cinoxacin INN

Presentation

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Contra-indications

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References

1. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), II, 1041. American Society for Microbiology, 1978.
2. Current Chemotherapy (Proceedings of the 10th International Congress of Chemotherapy), I, 704. American Society for Microbiology, 1978.
3. Proceedings of the 9th International Chemotherapy Congress, 1976, 5: 417.
4. Antimicrobial Agents and Chemotherapy, 1976, 9: 502.

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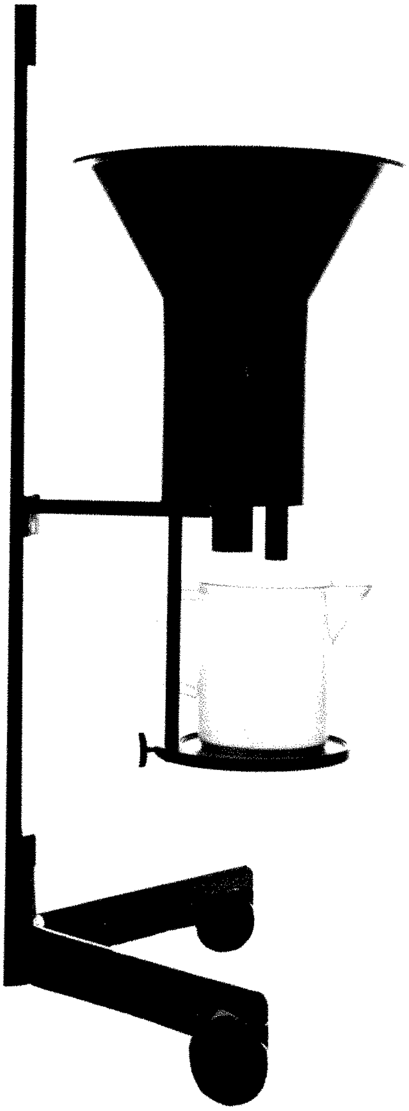

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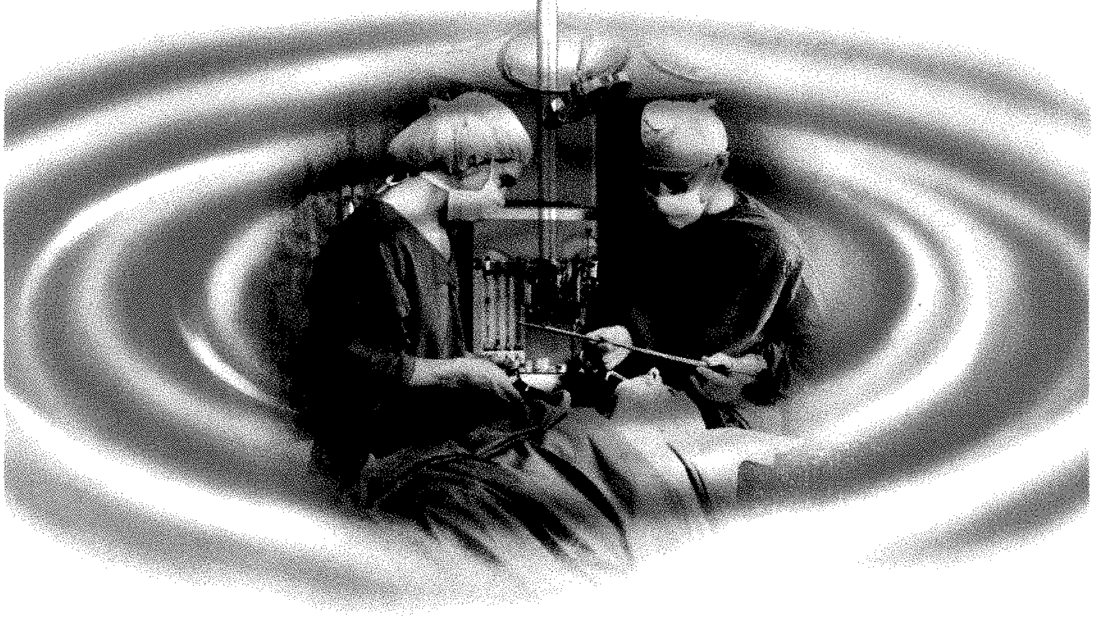

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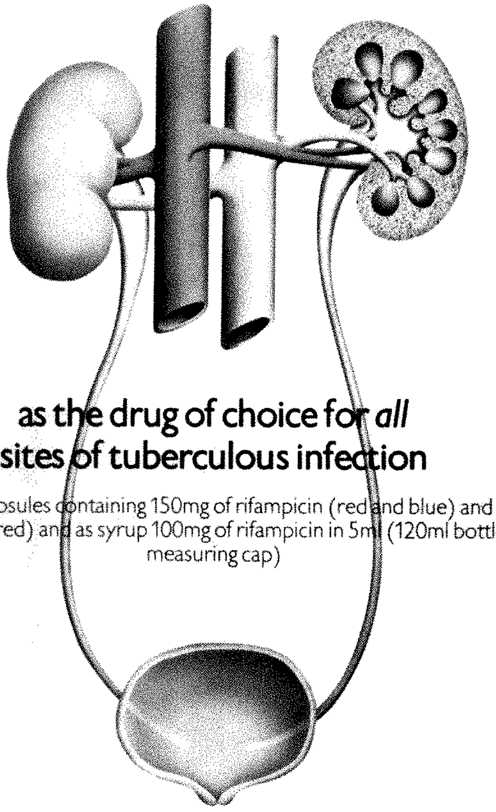

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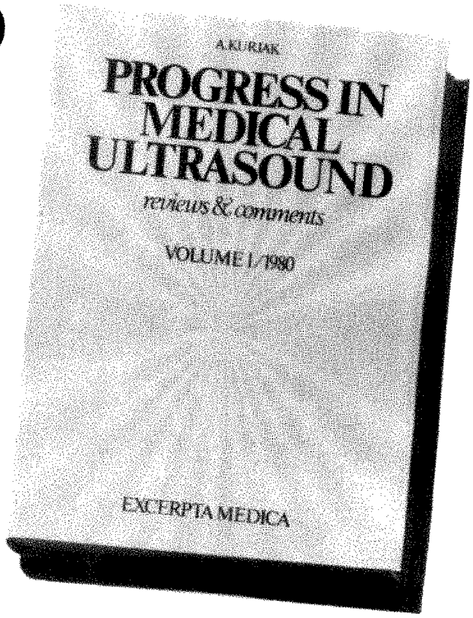

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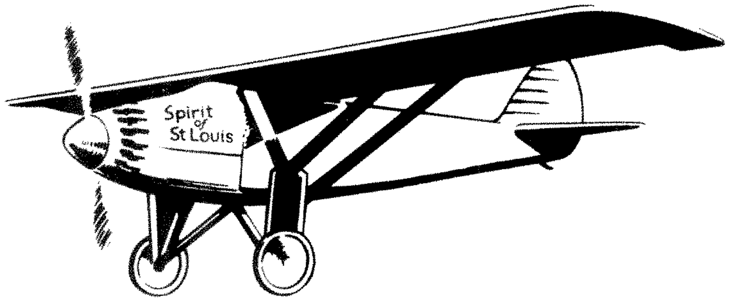

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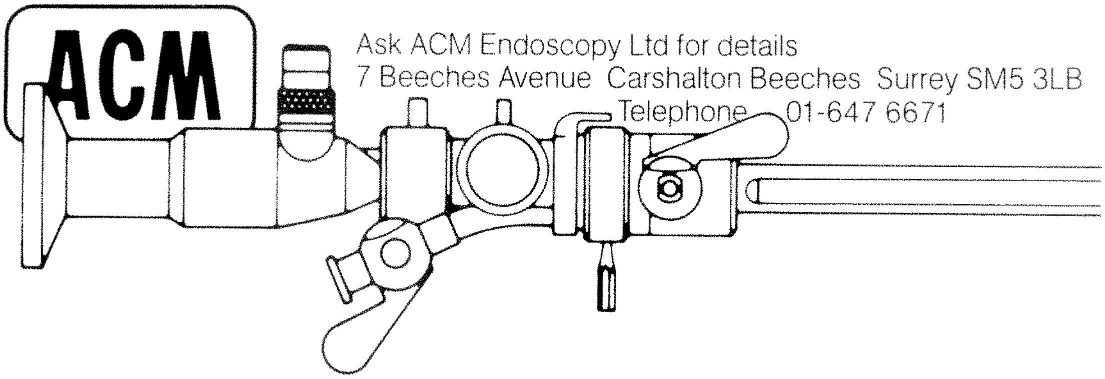

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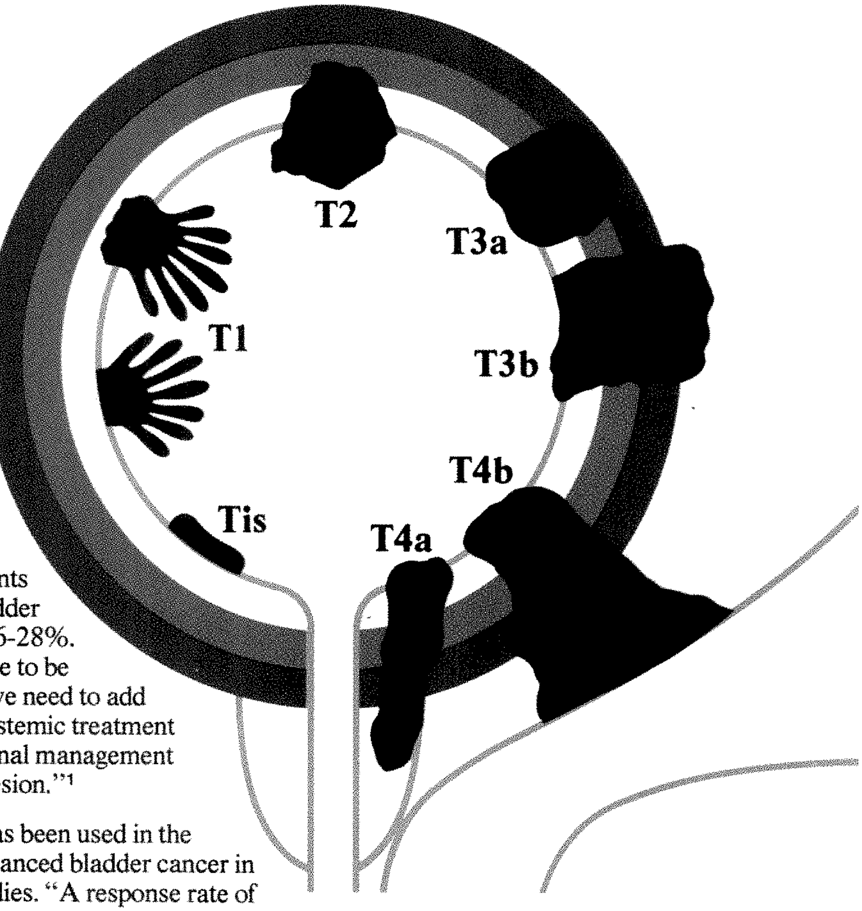

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2. *Brit. J. Urol. 1977, 49, 673*
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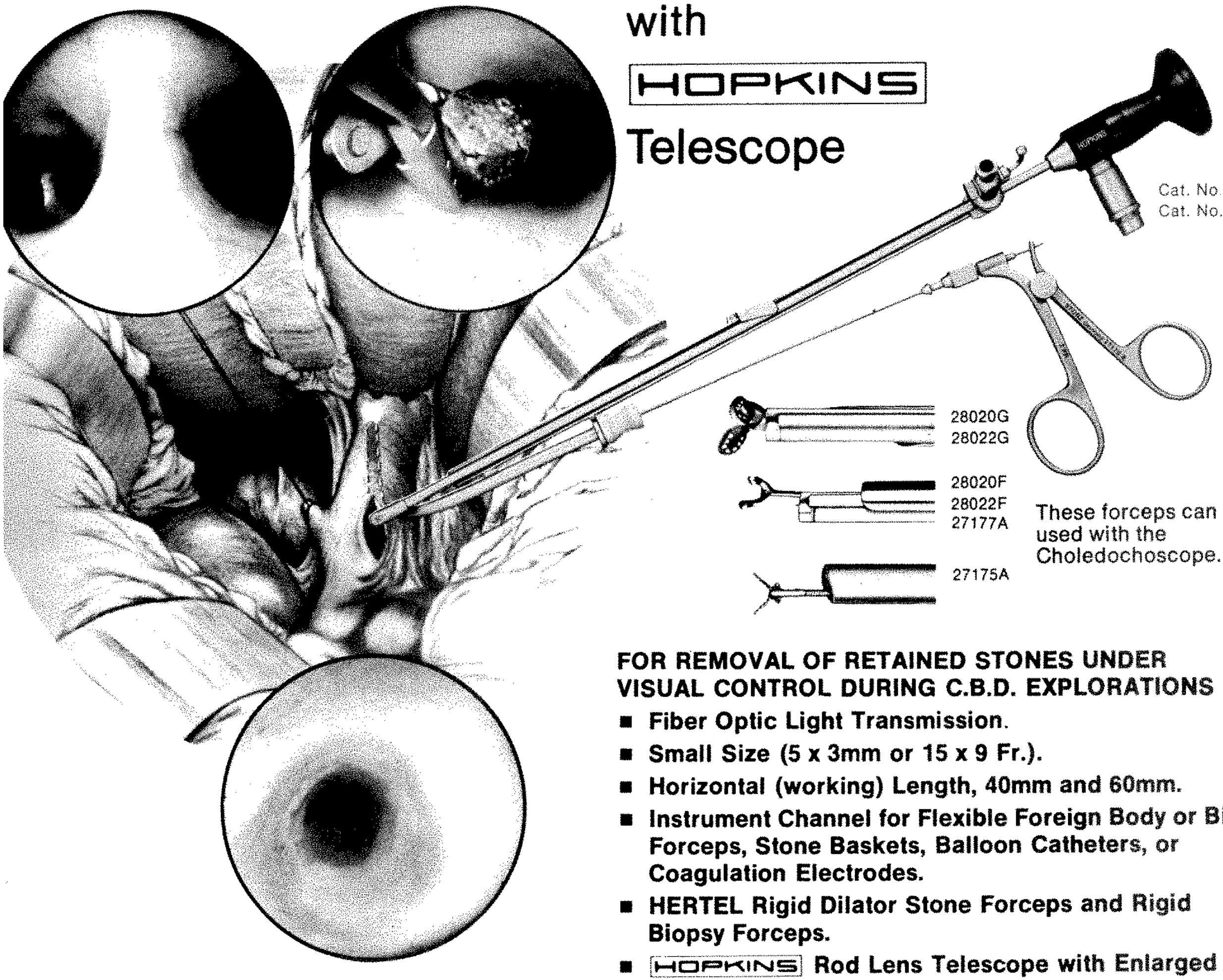

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Nephroscopy in Stone Surgery

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Summary—We present the results of our experience with the use of the nephroscope in 130 open procedures for removal of renal stones. The Storz rigid instrument was used and permitted visualisation of approximately 60% of calices and frequent identification of small stone fragments which would not otherwise have been seen. In 32 patients biopsies were taken on papillary epithelium. In 8, plaques of subepithelial calcification were identified. These were macroscopically obvious and widely distributed over the caliceal epithelium. A high proportion of the biopsies (66%) showed a chronic inflammatory cellular infiltrate which was not necessarily related to urinary infection. Such generalised changes again indicate the futility of partial resection in the management of renal stone disease.

Nephroscopy, *i.e.* visualisation of the intrarenal caliceal system, is not new. In 1925 Fuchs mentioned the use of a nephroscope during renal exploration. Early urologists had endoscoped the kidney via a nephrotomy, usually in cases with an established nephrostomy tube. Trattner (1948) described the visualisation of the intrarenal caliceal system with a straight nephroscope. In 1950, Leadbetter reported on the clinical use of a right-angle nephroscope. In the course of the past decade the first widely used nephroscope has been developed and a series of papers about operative nephroscopy has been published (Hertel, 1973, 1974; Gittes, 1976; Koff, 1976).

In 1975 Clark wrote: "Few urologists would operate upon a bladder without looking inside it first, but how many will look inside the kidney?" Since then, endoscopic therapy for stones and neoplasms of the biliary tract has gained increasing acceptance (Shore *et al.*, 1971; Shore, 1976; Tompkins *et al.*, 1976; Vosse, 1977).

We report our experience with nephroscopy and, in particular, the results of biopsy of renal papillae in patients with nephrolithiasis.

Patients and Methods

Patients

Since 1972 we have used the nephroscope in 130 renal stone operations. We used the Storz instrument in the majority of cases but also used the Wolf nephroscope.

The indications for operative nephroscopy were: staghorn calculi, small caliceal calculi, and stone cases with additional changes in the caliceal system, such as tumour-like lesions, ulceration, etc.

In 32 patients who underwent operation for renal stones during 1978 we performed a pyeloscopy and biopsied a renal papilla. The localisation of the renal stones was as follows: pelvis (10 cases), calix or infundibulum (11), pelvis and calix (1), staghorn calculi (10). Of the 32 patients 19 were female and 13 male. The youngest was 18, the oldest 84 years old. The average age was 44.4 (Table 1).

Method

Instrument The nephroscope is a small-calibre fibre-optic endoscope with a rigid shaft; the effectiveness of the irrigation system is of decisive importance. A simple saline intravenous solution is attached to the instrument. To achieve appropriate pressure and thereby adequate flow, we use a blood-pressure cuff which is placed around the infusion bag. In our experience the resulting pressure did not rupture fornices or cause extravasation of fluid. The pulsatile irrigation system with the dental Water-Pik instrument, which was previously used exclusively for direct irrigation of the calices, was abandoned because it caused papillary lesions.

Technique of Nephroscopy Any operative approach to the kidney can be used for nephroscopy.

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Table 1

Patient, age, sex	*Inflammation*	*Calcification*	*Urinary infection*	*Stones*
M.M., 31 (f)	+	−	+	1 staghorn
H.B., 69 (m)	−	−	−	2 pelvic
J.B., 37 (f)	−	+	−	1 large pelvic
G.D., 54 (f)	+	−	−	Staghorn
A.S., 59 (f)	+	−	+	Staghorn
A.W., 60 (m)	−	+	−	2 caliceal 1 pelvic
E.K., 28 (m)	+	−	−	Staghorn
A.S., 28 (m)	+	−	−	1 pelvic
J.K., 33 (f)	+	−	+	1 pelvic
E.S., 56 (f)	+	−	+	2 caliceal
H.Z., 37 (m)	−	−	−	2 pelvic
A.G., 35 (m)	−	+	−	1 infundibular
H.V., 64 (f)	+	−	−	1 pelvic
V.S., 27 (f)	+	−	+	1 infundibular
V.W., 45 (f)	+	+	+	Staghorn
K.H., 48 (f)	+	−	+	2 caliceal
C.F., 37 (m)	−	−	−	2 infundibular
A.W., 57 (f)	+	+	+	1 infundibular
A.S., 86 (m)	+	−	+	2 caliceal
H.S., 34 (f)	+	−	+	Staghorn
E.M., 52 (m)	+	−	−	Staghorn
D.B., 43 (f)	−	−	−	1 pelvic
M.R., 29 (f)	+	−	−	Multiple caliceal
E.W., 50 (f)	+	+	+	Staghorn
G.S., 53 (f)	+	−	−	1 infundibular
H.K., 40 (f)	+	−	−	Staghorn
E.B., 47 (f)	−	−	−	1 infundibular
G.F., 69 (m)	−	+	−	1 pelvic
M.Z., 50 (m)	−	−	−	Multiple caliceal
R.B., 20 (m)	+	−	−	1 pelvic
R.S., 62 (m)	−	+	−	Multiple pelvic
N.T., 46 (f)	+	−	+	Staghorn

Logically, an extrarenal pelvis is more advantageous for endoscopy than an intrarenal pelvis. Initially we introduced the nephroscope through a very small pyelotomy, thinking that this would facilitate dilatation with the irrigation and thus improve visualisation of the calices. Experience, however, showed that an ample transverse pyelotomy was the better method for clear visualisation of the pelvis.

In most cases, especially in those with staghorn calculi, we performed a Gil-Vernet exposure, a transverse pyelotomy and an extraction of the major parts of the stones. Then we introduced the nephroscope and explored the calices. As a result of irrigation the calices were easily displayed and the irrigation fluid drained unobstructed through the wide pyelotomy. Mucosal oedema and epithelial shreds inside the kidney could, however, impair vision and it was possible to overlook the caliceal entrance. In every case of multiple stones in which we used the nephroscope, an intra-operative X-ray of the kidney was performed.

Biopsies

The biopsy of a renal papilla in cases of caliceal stones was performed on the papilla of the stone-bearing calix and in the other cases on papillae from the lower or middle caliceal system.

During histological examination special care was taken to detect calcification and chronic inflammation. In all cases a bacteriological examination of the urine was performed pre-operatively. Particular attention was paid to the relationships between inflammation, calcification and the presence of bacteriuria.

Results

Nephroscopy

Experience in nephroscopy of 130 patients has shown that this is an auxiliary procedure which is mainly of use in complicated stone surgery. It permits visualisation of approximately 60% of the calices and the localisation of small stone fragments. Nephroscopy is not a substitute for intra-operative X-ray. However, caliceal stones with a diameter less than 2 mm are difficult to visualise both pre-operatively and post-operatively. With the nephroscope these small stone fragments and organic debris can be seen and irrigated under direct vision.

Furthermore, the method is of value in the diagnosis of additional disease in the calices and pelvis such as calcified papillae, inflammation, ulceration or concomitant tumour.

Complications Between 1972 and 1977 we have had no serious complications such as intra-operative or post-operative bleeding, parenchymal injury or damage to the pelvis or calices. In a recent case we did a pyeloscopy and biopsy of the papilla. Post-operatively we encountered massive bleeding and were forced to re-operate and do a small partial resection of the bleeding part of the kidney.

In general, the operative procedure is prolonged for approximately 10 to 20 min by nephroscopy, but this has not resulted in a higher infection rate in our series.

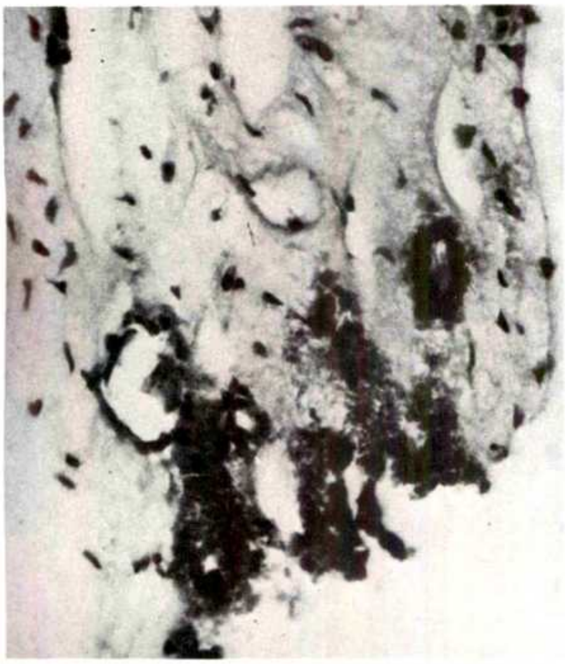

Fig. 1 Subendothelial calcifications along the collecting tubes (H and E ×500).

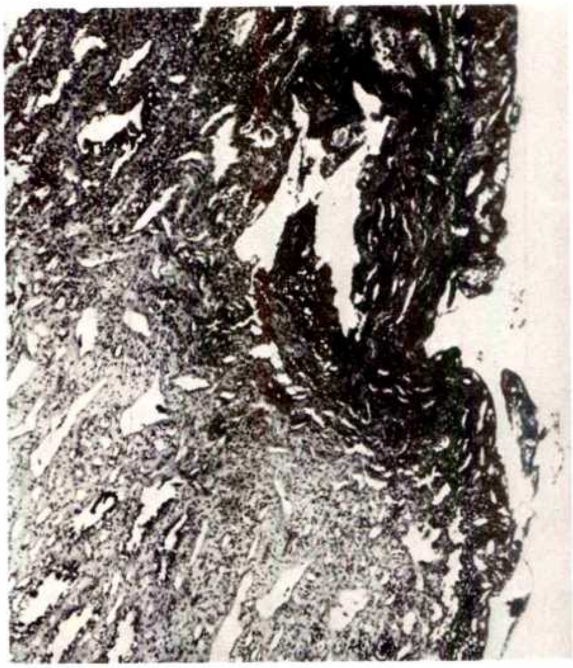

Fig. 2 Partial necrosis and ulcerations at the tip of the papilla. Massive infiltration of round cells (H and E ×80).

Biopsies of Renal Papillae

Eight out of 32 biopsies revealed unquestionable, partly submucosal, partly subendothelial calcification along the collecting tubes (Fig. 1). This finding corresponded nephroscopically to tiny whitish-yellow plaques distributed over most of the papillae. Twenty-one cases, *i.e.* 66% of the biopsies, showed typical signs of chronic interstitial inflammation with an increase of connective tissue and massive infiltration of round cells (Fig. 2). Of these 21 biopsies with chronic inflammation, 12 were seen in patients with significant urinary infection. In the other 9, histologically confirmed changes due to inflammation were found, but no urinary infection had been diagnosed clinically, either pre-operatively or post-operatively (Table 2).

In staghorn calculi we did 10 biopsies. Chronic inflammation, in some cases severe, was revealed in all of the 10 specimens, although significant

Table 2

Total biopsies	*Calcification*	*Chronic inflammation*	
32 (100%)	*8 (25%)*	*21 (56%)*	
		urin. inf.	no urin. inf.
		12 (37.5%)	9 (28.1%)

urinary infection was seen in only 6 of them. Here also, 2 biopsies of papillae showed typical calcification.

Discussion

The advantages of nephroscopy are as follows: visualisation of the upper, lower and (to a certain degree) the middle caliceal system and detection of residual stones; easier removal of small caliceal stones without blind probing and manipulation with forceps and, in general, less trauma to the kidney; assessment not only of the stone situation but also of the condition of the papilla.

It is, however, not always certain that all calices within a kidney have been visualised. This is especially true in the case of a kidney which is difficult to mobilise fully, *e.g.* one which has previously been operated on. One should learn a systematic inspection procedure similar to that of cystoscopy. However, even if the examination is performed systematically, it is sometimes difficult to maintain orientation. According to published data, about 60 to 90% of the calices may be visualised. In our experience we could explore most of the calices of the upper and lower segment, and about two-thirds of all calices of each kidney.

The technical development of the stone forceps is not yet completely satisfactory in that small stones, although localised, cannot always be grasped. In handling the forceps we have encountered problems when (1) the infundibulum is too small to reinsert the nephroscope with forceps, (2) the stone lies in an angle which cannot be reached by the instrument, or (3) the stone is too large to pass through the infundibulum safely.

Our biopsy studies confirmed established facts. No less than 66% (21 cases) of the 32 patients examined showed evidence of chronic inflammation. Of these 21, only 12 cases also had significant urinary infection, the other 9 having had sterile urine even in their previous case history. In these cases the stone, as a foreign body, may well have induced clinically irrelevant infections which were then revealed as corresponding histological manifestations. In all cases of staghorn calculi, clear-cut inflammatory changes are found in the parenchyma of the kidney. Multiple small calcifications were found in 25% of our cases (Fig. 3). Calcification within a renal papilla is a very common finding. Haggitt and Pitcock (1971) found varying degrees of medullary calcification in all of 100 kidneys from randomly selected patients. Typical subepithelial Randall's plaques were present in 23%. The prevalence of Randall's plaques reported in the literature ranges between 17 and 35% (Prien, 1975).

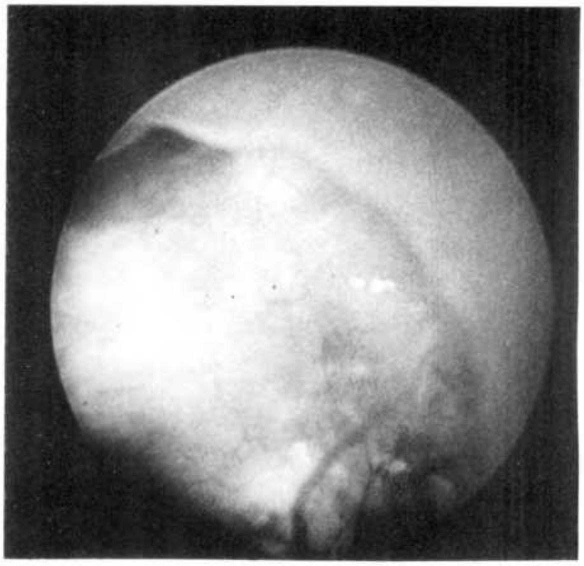

Fig. 3 Nephroscopy: calcifications in a renal papilla.

These plaques are widely distributed all over the renal papillae and are not limited to the stone-bearing calices. Because of their purely incidental distribution, the plaques in a stone-bearing calix do not justify resection of renal parenchyma. This is particularly true for lower pole stones with papillary calcifications. Following analysis of the sequelae of 131 partial nephrectomies, Wald *et al.* (1978) concluded that partial nephrectomy cannot be recommended for the removal of a hypothetical stone-forming segment of the kidney.

The circumscribed resection of calcified papillae is not indicated either, for in our experience too many papillae in a given kidney are involved. Complete removal of all plaques is not possible and would cause excessive loss of parenchyma.

It has not yet been established whether patients with plaque-bearing kidneys form recurrent stones more frequently than those without plaques. This question is currently being investigated.

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A Conservative Approach to the Management of Blunt Renal Trauma

Results of a Follow-up Study

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Summary—Forty patients with abnormal radiological findings after blunt renal trauma are presented. A conservative approach to treatment led to only 3 nephrectomies in patients with renal pedicle injury and to surgery in another 4 patients; in only one case was the function of the injured kidney reduced. At follow-up 1 to 5 years later, 4 patients had mild subjective symptoms but the objective findings were few and insignificant.

However, since serious sequelae (*e.g.* hypertension) may follow renal trauma, we suggest that these patients should be seen one year after injury for clinical examination, including renography and measurement of blood pressure.

Renal injury caused by blunt trauma may be divided into 4 groups (Hessel and Smith, 1974): (1) contusion, (2) laceration, (3) shattered kidney and (4) pedicle injury. The therapeutic approach to lesions in groups 1, 3 and 4 has now gained general acceptance, but controversy still exists in the laceration group. Some recommend surgery (Hodges *et al.*, 1957), others a conservative approach (Hai *et al.*, 1977; Mendez, 1977; Thomson *et al.*, 1977; Wein *et al.*, 1977).

There is little information in the literature concerning late complications (Nilsson and Sandberg, 1962; Hessel and Smith, 1974; Mendez, 1977). The present study reports our experience with a conservative approach to blunt renal trauma and the results of a follow-up examination 1 to 5 years later.

Materials and Methods

During the 5-year period 1970 to 1975, 76 patients with blunt renal trauma and haematuria were admitted to one of the 2 urological departments of the Copenhagen County Hospitals (patients with associated major injury were excluded).

In 36 cases the excretion urogram (EU) at admission was normal. These patients were not followed up and have been excluded from the study.

Data from the remaining 40 patients with abnormal excretion urograms on admission are shown in Table 1. The majority were young males injured in road traffic accidents or during sporting activities; only one patient sustained injury at work. More than three-quarters of the patients complained of pain or tenderness; 2 were in clinical shock, but in 3 cases haematuria was the only symptom.

Patients were assessed by routine high-dose EU with the exception of one patient, who was operated on immediately because of severe haemorrhagic shock (Table 2). Renal angiography was performed in 10 cases; in 2 patients with non-visualisation of the kidney on EU the renal artery

Table 1 Patient Data

		No.
Total patients		40
Male	29	
Female	11	
Age (years) range 6-64, median 18.		
Aetiology of trauma		
Road traffic accident		19
Sport		20
Work		1
Clinical signs and symptoms		
Haematuria	macroscopic	24
	microscopic	16
Abdominal or flank pain or tenderness		32
Mass		4
Shock		2
No symptoms		3

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Table 2 Urological Investigations During Hospitalisation

	No.
Routine excretion urography	39
Infusion pyelography with tomography	1
Renal arteriography	10
^{131}I-Hippuran renography	12

was thrombosed; in 2 other patients angiography showed separation of the kidney into 2 fragments (shattered kidney). In the remaining 6 patients the angiographic information did not lead to any change in treatment.

^{131}I-Hippuran renography (RNG) in 12 patients gave information on kidney function, but did not influence treatment.

In Table 3 the patients are classified according to Hessel and Smith (1974) and their treatment described. The majority were treated conservatively, only 7 being subjected to surgery. Two patients with laceration of the kidney had surgical exploration with drainage of perirenal extravasation, while 2 shattered kidneys were sutured and drained. Nephrectomy was performed in the 3 patients with pedicle injury. The mean stay in hospital was 10.5 days (range 2-27 days).

At follow-up the patients had a clinical examination, urine culture, determination of plasma creatinine concentration, ^{51}Cr-EDTA clearance, RNG and EU. The ^{51}Cr-EDTA clearance determination was carried out as described by Brøchner-Mortensen (1972); the RNG was classified as normal if 5 parameters were within the 95% confidence interval of the parameters from renograms of normal subjects (Mogensen *et al.*, 1975).

Table 3 Diagnosis and Treatment in 40 Patients with Blunt Renal Trauma and Radiographic Abnormalities

Diagnosis	*Treatment*		
	Conservative	*Surgery*	*Nephrectomy*
Contusion	19	0	0
Laceration	14	2	0
Shattered kidney	0	2	0
Vascular pedicle injuries	0	0	3

Table 4 Symptoms and Results of Urological Investigations in 33 Patients at a Median 39 Months (Range 6-78 Months) after Blunt Renal Trauma

	No.
Occasional slight flank pain or tenderness	4
Hypertension	2
Urine culture negative	33
Plasma creatinine concentration <120 mmol/l	33
^{51}Cr-EDTA clearance normal	33

Results of excretion urography (EU) and ^{131}I-Hippuran renography (RNG)*

		RNG	
		Normal	*Abnormal*
EU	Normal	17	4
	Abnormal	3	7

* In 2 patients only RNG was done; one was normal, the other abnormal.

Results

All patients were alive at the time of follow-up, but 3 did not attend (one with a contused kidney and 2 with lacerations). Four patients with kidney contusions refused to undergo the urological investigations; their clinical examination, including blood pressure, was normal. Thus the follow-up examination was carried out in 33 patients (83%) at a median 39 months (range 6-78 months) after the renal trauma (Table 4).

Four patients complained of mild, intermittent flank pain and 2 had mild hypertension. All patients had negative urine culture and normal total renal function.

The EU was normal in 21 patients, 4 having a slightly abnormal RNG; in one of these the injured kidney's share of total renal function was abnormal. Two patients refused to undergo EU; one had a normal RNG, the other an abnormal peak time but normal share of total renal function.

Ten patients had an abnormal EU. Three of these had had a nephrectomy, while 3 who had been treated conservatively for lacerated kidneys and 4 who had been operated on because of lacerated or shattered kidneys had minor sequelae such as caliectasia or caliceal cysts. In 3 patients the RNGs were normal; in 4 patients the RNG showed no function (nephrectomised) or abnormally low function of the kidney, while 3 patients had other renographic abnormalities.

Discussion

Excretion urography is mandatory in all patients with a history of renal trauma in order to classify the renal injury and the status of the contralateral kidney. Routine high-dose EU alone gave sufficient information to determine treatment in 35 of the 39 patients. Two of these, in whom renal angiography did not add further information, had a lacerated kidney explored and the haematoma drained. In the remaining 4 patients renal angiography was necessary for the diagnosis of renal artery thrombosis (non-visualisation of the kidney on EU) or shattered kidney (lack of exact information about the renal architecture on EU).

Our figures confirm the results of Hessel and Smith (1974) who, in an exhaustive review of the literature, found the average diagnostic accuracy of high-dose EU in blunt renal trauma to be 91%. With routine tomography the degree of accuracy may be even higher. Angiography can no doubt provide the most accurate anatomical diagnosis of renal injury. However, we agree with Lipsky *et al.* (1976) and Wein *et al.* (1977) that the indications for renal angiography are limited, *i.e.* non-visualisation of the kidney or suspicion of more severe injury than seen on the EU. Our experience shows that this practice will lead to minor sequelae in only a few cases.

The attitude to treatment in the present series was conservative. None of the contused kidneys was explored and only 2 of 16 patients with lacerated kidneys and retroperitoneal haematomas and/or urinary extravasation had the accumulation drained. Two patients with shattered kidneys had a renorrhaphy or polar resection, and in 3 patients with pedicle injury a nephrectomy was performed. Despite the expectant, non-operative management of the majority of patients, their stay in hospital was short. This approach to treatment entailed few complications. At follow-up, total renal function was normal and urine culture negative in all patients investigated. In 21 of 31 patients, including 9 with lacerated kidneys, the EU was normal. One of these patients had slightly reduced function of the injured kidney estimated from renography and another 3 patients had renograms showing partial obstructive uropathy. These findings can be explained by RNG being a more sensitive method for revealing individual kidney function and urinary tract obstruction than EU (Mogensen *et al.*, 1972; Mogensen *et al.*, 1976).

Apart from the 3 patients who underwent nephrectomy, minor radiological defects were found in 3 who were treated conservatively and in 4 who underwent surgery. In only one of the patients not treated by nephrectomy was the share of function of the injured kidney reduced (to one-third of total renal function). Three patients with small caliceal filling defects on EU had a normal RNG.

Mild hypertension was found in 2 patients at follow-up. The first was a 21-year-old woman who at admission had a lacerated kidney and signs of pyelonephritis in the contralateral kidney and who was treated conservatively. Control EU was suggestive of bilateral pyelonephritis; the urine was sterile and the glomerular filtration rate (GFR) was normal and equally distributed between the kidneys, assessed at renography as not having unilateral renal disease. The other patient was a 50-year-old man who had a perirenal haematoma drained. At follow-up, EU showed defects in the caliceal filling; the RNG was abnormal but showed a normal share of function between the kidneys. Investigations in both patients, including measurement of plasma renin activity, suggested that there was no relation between the renal trauma and the hypertension.

Follow-up of 40 patients 1 to 5 years after sustaining blunt renal trauma showed that a conservative approach to treatment led to mild subjective symptoms in 4 patients and insignificant objective sequelae in only a few cases. On the basis of the data we suggest that these patients should be followed up one year after injury by a clinical examination including measurement of blood pressure and isotope renography.

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The Parapelvic Renal Cyst

A Report of 8 Cases with Particular Emphasis on Diagnosis and Management

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Summary—The clinical, radiological and therapeutic aspects of 8 patients with parapelvic cyst of the kidney are reviewed.

The principal clinical features were either renal colic or dull loin pain. The main radiological findings consisted of a rounded smooth mass distorting the pelvis and elongating or dilating the calices. Complications were infection, stone, hypertension or hydronephrosis.

Operation was required in 6 patients, 2 of whom underwent nephrectomy.

In a review of renal cystic disorders Bernstein (1973) proposed that the classification of renal cysts should be based on associated phenomena rather than strict radiological or morphological criteria and he suggested 7 basic categories (Table 1).

Parapelvic cysts are of extraparenchymal origin and associated with lymphangiectasia or lymphatic obstruction (Bernstein, 1973). Eight patients with a parapelvic renal cyst are described in this study.

Patients

Between September 1974 and April 1978, 99 patients with cystic disorders of the kidney were admitted to our service. Eight of these patients had a parapelvic cyst and their main features are summarised in Table 2. Characteristic findings on intravenous or retrograde pyelography were (*a*) a rounded mass in the kidney, displacing the pelvis and calices, (*b*) a semilunar configuration of the pelvis, and (*c*) elongation and slight dilatation of the calices (Fig. 1). In one patient intravenous urography failed to show the upper calix, suggesting a malignant lesion, but on retrograde pyelography the calix was expanded, thus confirming the presence of a benign parapelvic cyst (Fig. 2). Nephroangiography provided a more accurate image of the size and location of the cyst (Fig. 3). We were unable to demonstrate calcification of the wall or interior of the cyst, although in 2 cases the cyst was associated with a renal stone on the affected side (Fig. 4).

Table 1 Classification of Renal Cystic Disorders in Summary (Bernstein, 1973)

A.	Renal dysplasia
B.	Polycystic disease
C.	Renal cysts in hereditary syndromes
D.	Renal cortical cysts
E.	Renal medullary cysts
F.	Miscellaneous intrarenal cysts
G.	Extraparenchymal renal cysts

Other complications of parapelvic cysts were infection of the cyst (1 case), infected hydronephrosis (1 case) and hypertension (1 case). This last patient was a 44-year-old woman who had

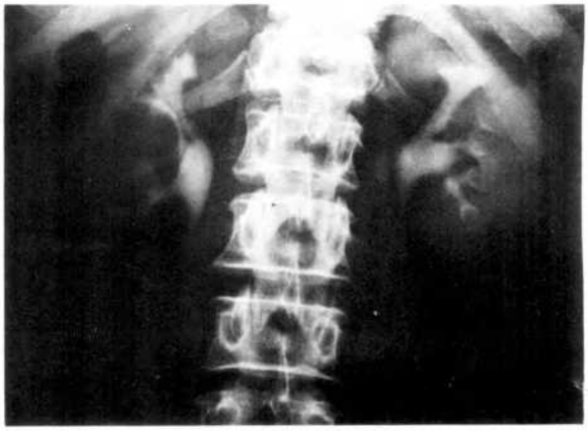

Fig. 1 Intravenous urogram showing parapelvic cyst of the right kidney.

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Table 2 Summary of Patients With Parapelvic Cysts of the Kidney (September 1974-April 1978)

	Sex, Age	*Main symptom*	*Radiology*	*Location*	*Complication*	*Management*
1	M, 68	Pain, 3 months	Upper pole "mass"	R	None	Operative: cyst puncture
2	F, 52	Pain, 3 months	Semilunar pelvis	R	None	Conservative
3	M, 40	Renal colic, 1 year	Semilunar pelvis, elongated calices	R	None	Operative: cyst excision
4	F, 65	Pain, fever, chills, 2 weeks	Renal "mass", hydronephrosis	L	Cyst suppuration	Operative: nephrectomy
5	M, 54	Renal colic, haematuria, 1 month	Semilunar pelvis, elongated calices, hydrocalicosis	L	Renal calculus	Operative: nephrectomy
6	F, 54	Renal colic, urinary infection, 8 months	Semilunar pelvis	L	Hydronephrosis, pyelonephritis	Operative: cyst excision
7	F, 49	Renal colic, haematuria, 3 months	Semilunar pelvis, elongated calices	L	Renal calculus	Conservative
8	F, 44	Renal colic, 3 months	Rotation of kidney	L	Hypertension	Operative: cyst excision

had left renal colic 3 months before admission. Intravenous pyelography revealed a "cystic-like lesion" in the left kidney (Fig. 5). When referred to our service her blood pressure was 160/110 mmHg and she insisted that she had been normotensive previously. After excision of a large parapelvic cyst her blood pressure fell to 140/100 mmHg and 3 months post-operatively her local physician reported that her blood pressure had returned to normal without antihypertensive treatment.

Of 6 patients who underwent operation, the cyst was excised in 3 and aspirated in one. In the other 2 cases nephrectomy was performed, in one because of an infected cyst and in the other because of associated stones.

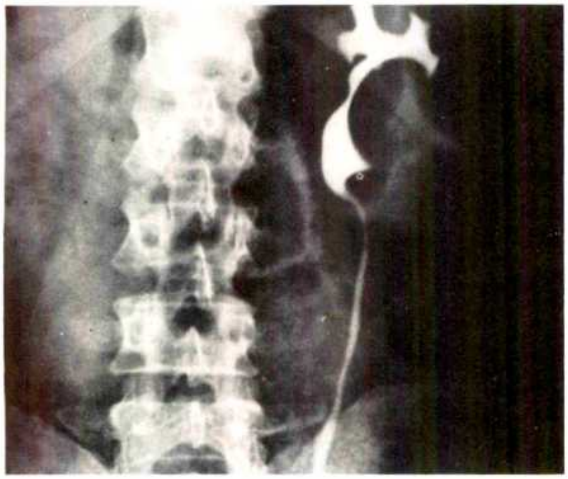

Fig. 2 Retrograde pyelogram showing the typical semilunar pelvis and elongated calices of a parapelvic cyst.

Discussion

Parapelvic renal cysts are benign and are caused by lymphatic obstruction or lymphangiectasia (Spence and Singleton, 1972; Bernstein, 1973). However, Deliveliotis and Kavadis (1969) pointed out that nephrectomy might be indicated because

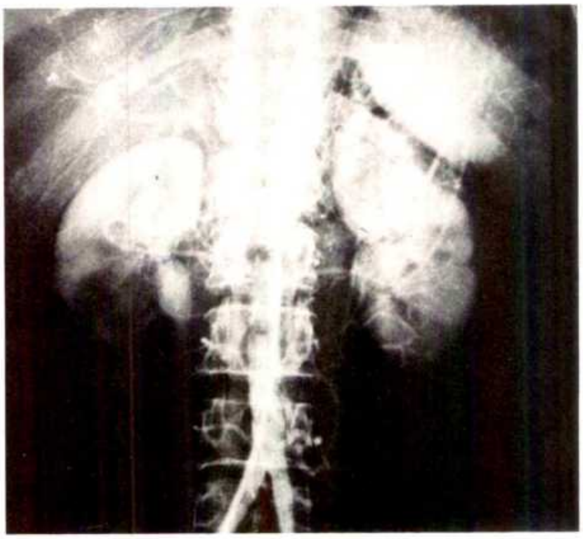

Fig. 3 Nephroangiography of the patient in Figure 1. The nephrographic phase clearly shows the size and location of the cyst, which is avascular.

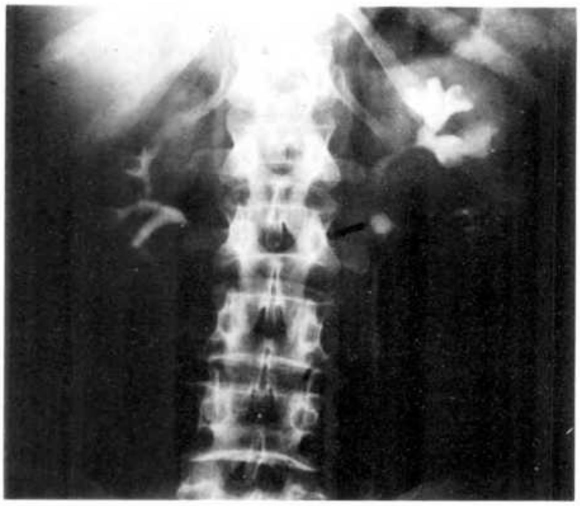

Fig. 4 Secondary renal lithiasis in a patient with a parapelvic cyst. The stone lies in the compressed semilunar pelvis.

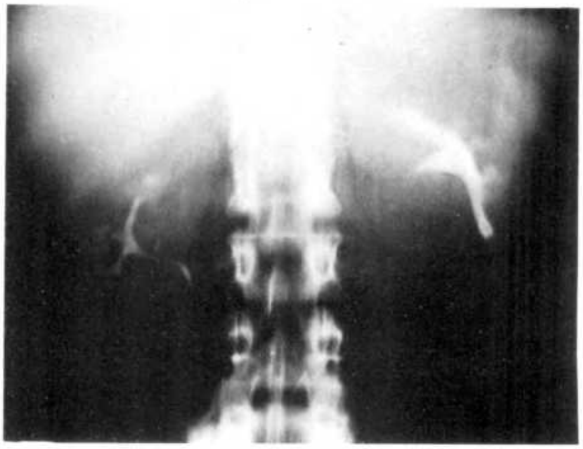

Fig. 5 Nephrotomography of a patient with a large parapelvic cyst of the left kidney which has rotated. Hypertension developed in this patient.

of concomitant pyelonephritis or operative difficulties.

All of our patients gave a brief history of symptoms related to the kidney. Of special interest was one patient who presented with an acute infection of the kidney due to spontaneous suppuration of the cyst and another (Fig. 5) who developed hypertension which disappeared when a large parapelvic cyst was removed (Babka *et al.*, 1974).

Intravenous urography with nephrotomography proved very useful in the investigation of parapelvic cysts. Renal scanning was of limited value in our investigations. Nephroangiography was required on only 2 occasions to confirm the avascular nature of the cystic mass and to identify its true size.

Two patients were treated without operation and have done well. We believe that in cases with fewer symptoms, satisfactory renal function and no sign of obstruction, a conservative regime is indicated.

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Ureteric Diverticula: Ureterodiverticular Reflux and Yo-yo Effect.

A Television Study with Spot Filming

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Summary—Two cases of ureteric diverticulum are presented. Repeated infective episodes were the main presenting features in one, whereas intermittent attacks of colicky pain brought the other patient in for clinical assessment. Fluoroscopic evaluation of the latter patient demonstrated free ureterodiverticular reflux and a yo-yo phenomenon. Following diverticulectomy the pain completely disappeared.

A ureteric diverticulum is a rare congenital anomaly of the upper urinary tract. It has been a subject of considerable debate with respect to its aetiology and diagnosis and various criteria have been used for differentiating a true diverticulum from other conditions (Culp, 1947). It is now generally accepted that a ureteric diverticulum represents a blind-ending branch of a bifid ureter (Rank *et al.*, 1960). Ureteric diverticula are susceptible to infection and stone formation and these complications most commonly cause the presenting symptoms. We present 2 patients with ureteric diverticula. Both complained of pain. In one this was due to infection; in the other it appeared to be caused by peristaltic dysfunction.

Case 1. S., a 14-year-old girl, presented with a history of colicky pains in the left flank of 6 months' duration; the pain was relieved by spasmolytic agents. The episodes were unaccompanied by any urinary complaints or fever. Her menstrual history was normal. Urine analysis showed 1 to 2 pus cells per high power field and a sterile culture. Excretion urography (Fig. 1) showed normal upper tracts apart from a diverticulum 2.5 cm in length arising from the upper part of the left ureter and extending superiorly. A cystogram was normal.

In the absence of established infection or of calculus disease as possible causes of pain, the ureter and the diverticulum were observed on fluoroscopy with spot films. The study showed free ureterodiverticular reflux and to-and-fro movement of contrast between the diverticulum and the proximal ureter. The 2 limbs remained opacified, even on subsequent spot films, without the contrast entering the distal ureter (Figs. 2a and b). The girl was kept under observation for one year but she continued to have attacks of pain. The diverticulum was excised and she has remained pain-free.

Case 2. S.S., a 34-year-old man, complained of frequent attacks of dysuria, fever and chills for 3 years. Physical examination was unremarkable. Urine analysis showed 4 to 5 pus cells per high power field but culture was sterile since the patient was on antibiotics. An excretory urogram showed normal upper tracts except for a diverticulum 5 cm in length alongside the upper

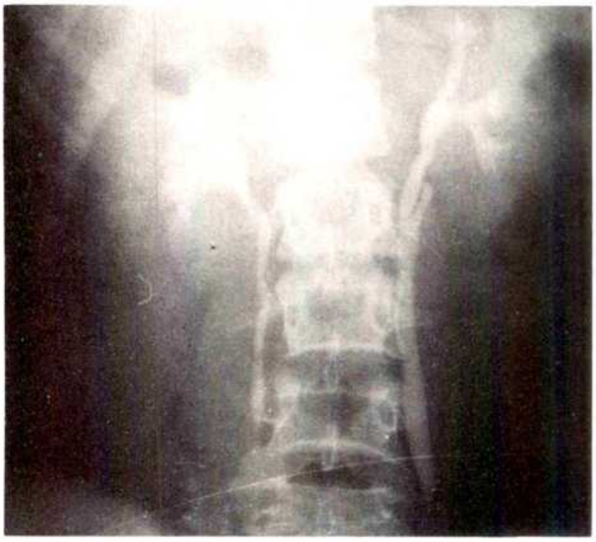

Fig. 1 Case 1. Excretory urogram showing a 2.5 cm diverticulum from the upper left ureter.

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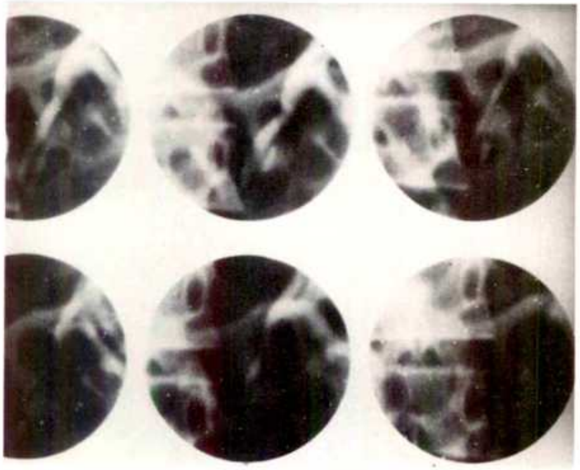

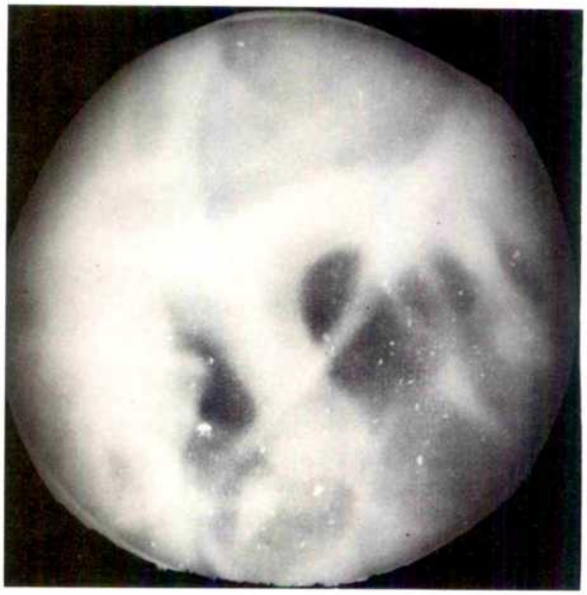

Fig. 2 (a) Case 1. Spot films visualising the peristaltic activity on television. There is ureterodiverticular reflux. The contrast does not enter the ureter below in any of the films. When the diverticulum contracts, the contrast again enters the proximal limb. (b) Case 1. A close-up of the same.

right ureter. The diverticulum extended proximally and joined the ureter below the third lumbar transverse process (Figs. 3 and 4). Since the urine culture was sterile and the diverticulum drained completely, no surgery was considered necessary.

Discussion

A congenital diverticulum of the ureter and a blind-ending branch of a bifid ureter result from premature cleavage of the ureteric bud (Culp, 1947; Rank *et al.*, 1960). A diverticulum may, however, be altered in shape by disease or pressure changes (Crumplin and Jones, 1972). In contrast, multiple ureteric diverticula appear to be acquired and have a definite cause and effect relationship with infection (Bothe and Cristol, 1942; Rank *et al.*, 1960). Rarely, they may be of congenital origin (Williams and Goodwin, 1965).

Ureteroureteric or pyelopelvic reflux have been described in association with duplicated renal collecting systems (Campbell, 1967; Amar, 1968; Tresidder *et al.*, 1970). Radiology reveals that asynchronous peristaltic waves are propagated from one limb of the duplex system into the other rather than down the ureter. The resting pressure in the common ureteric stem is always higher than that in either of the 2 proximal limbs, so that a functional obstruction is produced (Lenaghan, 1962; Olsson and Chute, 1971).

Our first patient demonstrated this free ureterodiverticular reflux and yo-yo peristaltic activity (Figs. 2a and b). Disappearance of pain following diverticulectomy is ample evidence that this peristaltic dysfunction was responsible.

Although our second patient has intermittent urinary tract infections, these are well controlled with antibiotics and surgical treatment is unwarranted at present.

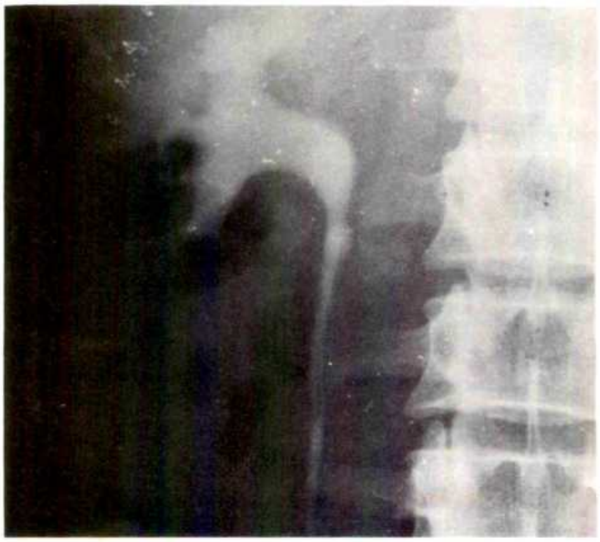

Fig. 3 Case 2. Excretory urogram showing a diverticulum medial to the upper right ureter.

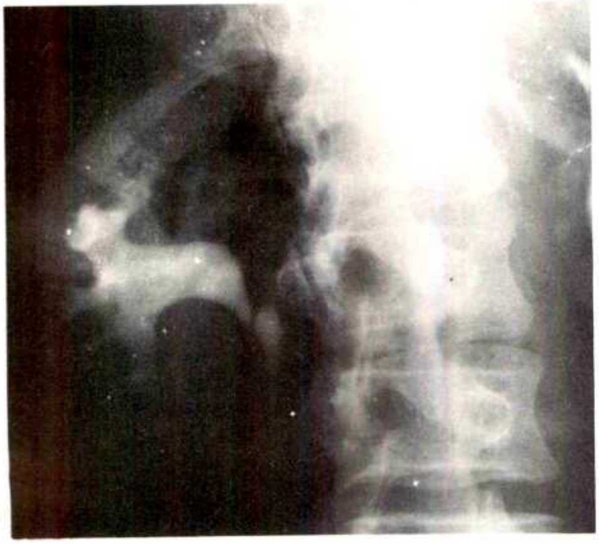

Fig. 4 Case 2. Lateral film showing the diverticulum more clearly.

We believe that symptomatic ureteric diverticula, in the absence of infection or stone disease, should be evaluated by fluoroscopy for evidence of ureterodiverticular reflux and peristaltic dysfunction. This should help in deciding which patients are likely to benefit from surgical intervention.

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Third Report on the Standardisation of Terminology of Lower Urinary Tract Function

Procedures related to the evaluation of micturition: Pressure-flow relationships. Residual urine

PRODUCED BY THE INTERNATIONAL CONTINENCE SOCIETY, FEBRUARY 1977*

Members: C. P. Bates, W. E. Bradley, E. S. Glen, D. Griffiths, H. Melchior, D. Rowan, A. Sterling and T. Hald (Chairman)

This report continues with recommendations on procedures related to the evaluation of micturition. It covers pressure-flow relationships and residual urine. These recommendations were subject to discussion during the Seventh Annual Meeting of the International Continence Society in Portoroz, Yugoslavia, September 1977.

These standards are proposed to facilitate comparison of results by investigators who use urodynamic methods. It is recommended that the aknowledgement of these standards in written publications be indicated by a footnote to the section "Methods and Material" or its equivalent: "Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted."

Pressure-flow relationships

To accomplish micturition a driving pressure is necessary. The driving pressure for micturition is the pressure within the bladder. This pressure can be generated by detrusor contraction (p_{det}), by abdominal pressure (p_{abd}) or by both ($p_{ves}=p_{det}+p_{abd}$). The urethra is an irregular and distensible conduit whose walls and surroundings, which have active and passive elements, influence the flow of urine through it. The bladder and urethra each have their own characteristics and in combination these characteristics determine the pressure-flow relationships of micturition. The relationships vary throughout a micturition and, in one individual, from one micturition to the next. Many attempts have been made to reduce the pressure-flow relationships to "urethral resistance factors" in an attempt to distinguish between normal and pathological conditions.

The following formulae have all been used at one time or another.

(1) p_{ves}/Q
(2) p_{ves}/Q^2
(3) $\sqrt{p_{ves}}/Q$
(4) p_{det}/Q
(5) p_{det}/Q^2
(6) $(P_{ves}-E_{str})/Q$
(7) $(p_{ves}-E_{str})/Q^2$
(8) $(p_{ves}-E_{str})p_{ves}$
(9) $d_{ura,\,eff}=\left[\frac{32\varrho f l Q^2}{\Delta p g \pi^2}\right]^{0,2}$

E_{str} is the kinetic energy per unit volume in the external stream, sometimes (unfortunately) called the "exit pressure", and $d_{ura,\,eff}$ is a calculated "effective urethral diameter".

ϱ = density of fluid
f = Fanning's friction factor
l = urethral length
Δ_p = friction loss
g = acceleration due to gravity.

Ideally we should like to choose the most useful of the above formulae and recommend it for general use. However, all of them originate from rigid tube hydrodynamics. The urethra is not a rigid tube. Therefore these factors vary not only during micturition but also from one micturition to another and so cannot provide a valid comparison between patients. They may even be misleading.

However, pressure-flow studies are still valuable

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* Revised following discussion during the business meeting of the International Continence Society, Portoroz, Yugoslavia, September 1977. Reprinted from *Scandinavian Journal of Urology and Nephrology* (1978) **12**, 191-193.

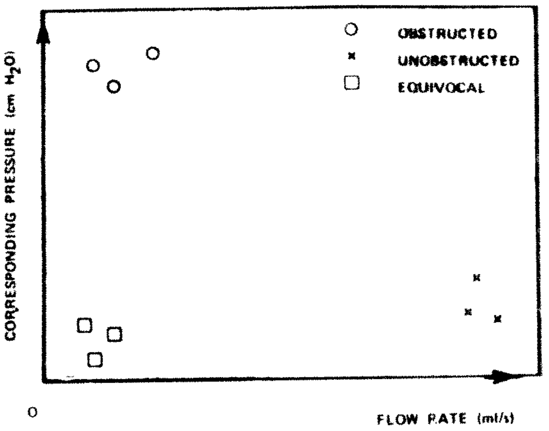

Fig. Recommended presentation of pressure-flow relationships. The points shown are purely illustrative to indicate how the data might fall into groups.

since some characteristic pressure-flow patterns may be identified. For example:

(*a*) Low flow rate accompanied by high pressure indicates obstruction.

(*b*) High flow rate accompanied by low pressure indicates freedom from obstruction.

(*c*) Intermittent flow rate associated with abdominal contractions and absence of detrusor activity indicates motor impairment of the detrusor.

(*d*) Intermittent interruptions of the flow in the absence of abdominal straining, with concomitant increases in the intravesical pressure, indicate intermittent contractions of the urethral and/or periurethral striated musculature.

In all cases the urodynamic findings should be assessed in conjunction with the results of routine urological investigations.

Presentation of pressure-flow relationships

It is suggested that it is more useful to present both the flow rate and the corresponding intravesical or detrusor pressure (p_{ves} or p_{det}), rather than to rely on a "urethral resistance factor". It is common to relate the maximum flow rate to the pressure at maximum flow, but any instant during micturition can be examined in the way proposed.

When presenting data from a group of patients, pressure-flow relationships may be shown on a graph as illustrated in the Figure. This form of presentation allows lines of demarcation to be drawn on the graph to separate the results according to the problem being studied. The points shown in the figure are purely illustrative to indicate how the data might fall into groups. The group of equivocal results might include either an unrepresentative micturition in an obstructed or an unobstructed patient, or detrusor insufficiency with or without obstruction. This is the group which invalidates the use of "urethral resistance factors".

Residual urine

Residual urine is defined as the volume of fluid remaining in the bladder immediately following the completion of micturition. The measurement of residual urine forms an integral part of the study of micturition. It is commonly estimated by the following methods:

(1) Palpation.
(2) Catheter or cystoscope: (i) transurethral, (ii) suprapubic.
(3) Radiography: (i) intravenous urography, (ii) micturition cystography.
(4) Ultrasonics: (i) A-scan, (ii) B-scan.
(5) Radioisotopes: (i) clearance, (ii) gamma camera.

Residual urine may result from various causes, such as detrusor insufficiency, infravesical obstruction or psychological inhibition. In the condition of vesicoureteric reflux, urine may re-enter the bladder after micturition and may falsely be interpreted as residual urine. The presence of urine in bladder diverticula following micturition presents special problems of interpretation, since a diverticulum may be regarded either as part of the bladder cavity or as outside the functioning bladder.

The methods mentioned above each have limitations as to their applicability and accuracy in the various conditions associated with residual urine. Therefore it is necessary to choose a method appropriate to the clinical problem.

The absence of residual urine is an observation of clinical value. An isolated finding of residual urine requires confirmation before being considered significant. The absence of residual urine does not exclude the possibility of bladder dysfunction or infravesical obstruction.

In infravesical obstruction there is a variable and poorly understood connection between the occurrence of residual urine and abnormalities in the pressure-flow relationships. In the study of this condition both need to be taken into account and their interrelation could be a fruitful area for future research.

Previous Reports

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Intravesical Prostaglandin: Release and Effect of Bladder Instillation on some Micturition Parameters

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Summary—Bladder washout effluent fluid was examined for prostaglandin-like activity following acidic lipid extraction and bioassay using the rat-stomach strips technique. A low basal level of prostaglandin-like material was detected in washouts collected when the bladder was empty in 4 out of 7 dogs. Increased levels were detected following micturition in 5 of these 7 dogs. A significantly high level of prostaglandin-like material was recovered after pelvic nerve stimulation. The prostaglandin-like material was tentatively identified as PGE based on the bioassay with the addition of specific antibody. Intravesically administered PGE_2 or $PFG_{2\alpha}$ significantly reduced, in a dose-dependent response, the threshold micturition volume. All of these findings suggested that prostaglandins may play a role in the micturition process.

Prostaglandins (PGs) were shown to be released into the blood stream in dogs during and immediately after bladder distension (Gilmore and Vane, 1971; Ghoneim *et al.*, 1976). Prostaglandin-like material of the E-series was also detected in the bath fluid during *in vitro* experiments on rabbit detrusor muscle strips (Bultitude *et al.*, 1976). Gilmore and Vane (1971) suggested that prostaglandins are released in the bladder to help it accommodate to stretch. They concluded that locally released PGs may overflow to reach the blood stream. The detrusor muscle exhibits excitatory changes to exogenously applied PGs, either added to the bath fluid (Ambache and Zar, 1970) or administered intra-arterially (Taira, 1974).

These observations raised certain questions: (*a*) Are PGs also released into the bladder cavity following bladder distension or stimulation of its motor nerve supply? (*b*) What is the effect of intravesically instilled PGs on voiding? In this study we attempted to answer these questions and to evaluate the possible physiological role and the therapeutic implications of PGs in micturition.

Material and Methods

Nineteen female non-pregnant mongrel dogs (12-16 kg weight) were anaesthetised with intravenous α-chloralose-urethane solution (100 and 500 mg/kg respectively) in saline. After endotracheal intubation, respiration was mechanically controlled by a pump with oxygen flow at 2 l/min. After episiotomy, the urinary bladder was exposed trans-abdominally and 2 polyethylene tubes (6 FG) were inserted through the dome into its cavity, one to record the intravesical pressure and the other to fill and empty the bladder. Both ureters were divided above the bladder and the urine was diverted to the exterior by 2 polyethylene tubes. This ensured exclusion of renal PGs and maintained bladder volume by external infusion. A femoral artery was cannulated for measurement of blood pressure. The urethral pressure was measured by one membrane chamber of a multichannel membrane catheter (Heyer-Schulte Co., California) positioned in the proximal half of the urethra at the site of the maximum pressure. The catheter was secured in place by a stitch placed near the external meatus. Changes in the intra-abdominal pressure were measured by a balloon rectal catheter. Urinary flow was measured by a flowmeter based on the principle of air displacement (model UF-2, Physico-Medical Corporation, Montreal). Pressure-measuring catheters were connected to Statham pressure transducers (P23 De) which, together with the flow sensor, were coupled to a multichannel pen recorder (Model 2500, Honeywell Corporation, Colorado).

Control voiding cycles were obtained by slow constant bladder filling with saline from an infusion pump (4-8 ml/min at room temperature).

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When a critical volume was reached (the threshold volume of micturition), reflux detrusor contraction occurred and micturition followed. Voiding cycles were repeated until reproducibility was assured, *i.e.* constant threshold micturition volume and constant pattern of urethrovesical pressure changes. In every experiment, each animal acted as its own control in depicting a change in the urodynamic parameters following PG infusion.

Study of the Release of PG-like Material into the Bladder Cavity

Seven dogs were used for this part of the study. After animal preparation as described, the bladder was evacuated of its contents. Bladder washouts, with physiological saline, were done until washings were colourless. After a waiting period of 15 to 20 min, with the bladder empty, a volume of saline equal to half of the threshold volume of micturition for each animal was slowly infused into the bladder (20-50 ml). The infused saline was kept in the bladder for 2 min and then collected in a sterile plastic container via the bladder cannula. Several samples of bladder washouts were obtained as follows:

(1) Control samples ($n = 12$). These were collected after the bladder was kept empty for 15 to 20 min.
(2) After reflex micturition and bladder evacuation ($n = 12$). Bladder washouts were done immediately after micturition and bladder evacuation.
(3) Before and after pelvic nerve stimulation (10 samples each). One intact pelvic nerve was exposed on one side of the bladder, stimulated by electrical pulses of 10 V and 0.2 ms duration at a frequency of 20 Hz for 2 s from a Grass stimulator (Model S4K). The bladder was half full at the time of the stimulation and voiding was complete. Immediately after voiding, an equal volume of saline was slowly infused into the bladder. This was collected after 2 min in plastic containers for PG bioassay.

The collected samples of bladder effluent were acidified to pH4 with 0.1 N HCI. Prostaglandins were extracted twice with ethyl acetate (2:1 V/V). The organic phase was evaporated under reduced pressure at 32°C and the residue was resuspended in 10 ml of oxygenated (95% O_2 + 5% CO_2) and warmed (37°C) Kreb's solution (Rioux *et al.*, 1977) and rapidly tested for PG-like activity on 2 rat stomach strips (Vane, 1957). The contraction of the stomach strips was measured with a force displacement transducer (Grass FT. 03) coupled to a Grass polygraph (model 79). A mixture of antagonists was added to the Kreb's solution in order to make the tissue strips specifically sensitive for detection and quantification of PG-like material (Gilmore *et al.*, 1968). The antagonists used included atropine, phentolamine, methysergide bimaleate and diphenhydramine (at a final concentration of 1.0×10^{-7} g/ml), oxprenolol (2.0×10^{-6} g/ml) and indomethacin (1×10^{-6} g/ml). Under these conditions, the contraction of the rat stomach strips by PGE$_2$ was rapid in onset (1-2 s) and completed within 60 to 90 s. The addition of indomethacin increases the sensitivity of the strips to exogenous PGE$_2$ (Eckenfels and Vane, 1972) and prevents the synthesis and release of PGs or PG endoperoxides by the tissue (Vane, 1971). The samples were assayed using known concentrations of PGE$_2$ as a standard and the results were expressed in terms of nanograms of PGE$_2$ equivalents per the whole bladder effluent sample. These values were uncorrected for recovery.

Mean values were determined for each experimental condition. The difference between the mean of any value and its corresponding control was analysed by Student's t-test for paired values. A P value of 0.05 or less was chosen for statistical significance.

Drugs. The following drugs were used: PGE$_2$ (Upjohn), indomethacin (Merck, Sharp and Dohme), atropine sulphate (Sigma), phentolamine HCl and oxprenolol (Ciba), methysergide bimaleate (Sandoz), diphenhydramine HCl (Parke Davis). A concentrated solution (10 mg/ml) of PGE$_2$ was made in absolute ethanol. Indomethacin was dissolved in 0.2 to 0.5 ml absolute ethanol. Appropriate dilution of all drugs was done in the Kreb's solution.

The Effect of PG

Twelve dogs were used for this part of the study. After obtaining reproducible control micturition cycles, PGF$_{2}\alpha$ and PGE$_2$ (in 6 experiments each) were infused into the bladder cavity in the saline used for bladder filling. PGE$_2$ was dissolved in absolute ethanol to obtain a stock solution containing 1 mg/ml, while PGF$_{2}\alpha$ was dissolved in distilled water at similar concentration of 1 mg/ml. These solutions were prepared fresh on the day of each experiment and appropriate dilutions were made in saline at the following dose concentrations: 0.03, 0.01, 0.3, 1.0 and 3.0 μg/ml saline).

Table 1 Release of PG-like Material in Bladder Washouts With Bladder Distension and Pelvic Nerve Stimulation*

Sample collection	*N*†	*Mean ± SEM*	*Range*
Bladder distension			
Empty bladder	12 (8)	2.8 ± 0.8	0-10
After micturition	12 (9)	4.7 ± 1.5	0-16
Pelvic nerve stimulation (PNS)			
Before PNS	10 (8)	3.3 ± 1.4‡	0-15
After PNS	10 (10)	23.0 ± 10.4‡	1.4-125

* Expressed as nanograms prostaglandin E_2 equivalents per whole bladder washout sample in 7 animals.

† Number of washout experiments in 7 animals. Number of samples containing PG-like material is indicated between parentheses.

‡ A significant difference exists between values marked ‡ (Student's t-test for paired values, $P < 0.05$).

Voiding cycles were repeated for each dose concentration. The parameters evaluated included maximum intravesical pressure, resting urethral pressure (before bladder filling), threshold micturition volume and duration of the micturition cycle.

Each animal served as its own control in calculating a change in any measured parameter of the voiding cycle. For each animal, the control value was considered as the unity for each subsequent value. The change in the value of each parameter at different dose concentrations from the control, for each PG, was analysed by an analysis of variance.

Results

Detection of Prostaglandin-like Material in Bladder Effluent Fluid

Control washout samples collected from the bladder under resting conditions contracted the rat stomach strips in the presence of antagonists to acetylcholine, 5-hydroxytryptamine, histamine and catecholamine in 8 out of 12 specimens. These 8 samples were collected from 4 animals. The PGE_2-like material assayed in all 12 washout samples was found to be 2.8 ± 0.8 ng per sample (mean ± SEM). Samples obtained following micturition contained higher values of PG-like activity: 4.7 ± 1.5 ng (mean ± SEM).

Washout samples obtained following pelvic nerve stimulation showed significantly higher values (23.0 ± 10.4; mean ± SEM) as compared to the control pre-stimulation values (3.3 ± 1.4; mean ± SEM). All of the 10 bladder effluent samples collected after pelvic nerve stimulation contained PG-like material (Table 1).

An attempt was made to determine whether the rat-stomach contracting activity of the bladder washout samples was due to PGs and which type of PGs. Specific antibodies raised against PGE_2 and $PGF_{2}\alpha$ in rabbits (Sigma) were added to 3 pooled samples in the bath after extraction. Contraction of the strips was completely blocked after the addition of PGE_2 antiserum and was not modified by the $PGF_{2}\alpha$ antibody.

Influence of Intravesically Administered $PGF_{2}\alpha$ and PGE_2

The effects of intravesically administered $PGF_{2}\alpha$ and PGE_2 (6 experiments each) are shown in Tables 2 and 3. Both PGs produced a significant ($P < 0.05$) reduction of the threshold micturition volume and of the micturition cycle time in a dose-dependent pattern. Insignificant changes of the intravesical and urethral pressures were observed. The minimal dose found to produce changes in the threshold micturition volume was 0.1 μg/ml saline for $PGF_{2}\alpha$ and 0.03 μg/ml saline for PGE_2.

Discussion

It is suggested from our experiments that PG-like material is released from the bladder wall and can be recovered in its lumen. Prostaglandin release induced by stretch has been shown to occur in organs other than the bladder, including the stomach (Bennett *et al.*, 1968), lungs (Piper and Vane, 1971), uterus (Horton *et al.*, 1971) and spleen (Gilmore *et al.*, 1968). The spontaneous release of PG into the nutrient bath fluid by muscle strips has also been reported for the bladder (Bultitude *et al.*, 1976), intestine (Vogt *et al.*, 1966) and uterus (Horton *et al.*, 1971).

It is generally accepted that PG release from

Table 2 Influence of Intravesical PGF$_2\alpha$ On Some Urodynamic Voiding Parameters*

	Control	*Intravesical PGF$_2$ dose (µg/ml saline)*					
	0.0	*0.03*	*0.1*	*0.3*	*1.0*	*3.0*	*P*‡
Maximum intravesical pres.	47.0	49.3 ± 3.1	54.0 ± 4.1	59.5 ± 5.9†	61.1 ± 8.2	55.6 ± 6.8	0.3
Urethral pres., resting	33.8	30.9 ± 2.3	39.4 ± 2.7	40.7 ± 2.9†	37.5 ± 2.9 †	34.9 ± 3.3 †	0.5
Threshold micturition vol. (ml)	77.1	81.5 ± 7.7	74.8 ± 6.5	63.9 ± 2.6†	61.6 ± 6.6 †	42.9 ± 6.5 †	<0.0001
Micturition cycle time (min)	11.7	11.5 ± 0.5	10.0 ± 0.7 †	9.0 ± 0.8†	8.0 ± 0.9 †	5.8 ± 0.9†	<0.0001

* Mean ± SEM values of 6 experiments. Pressure values are expressed in cmH_2O.

† A significant difference exists between values marked by † and their corresponding control as assessed by Student's t-test for paired values ($P < 0.05$).

‡ Associated probability for Fischer's analysis of variance; $P < 0.05$ is the level of significance.

tissues indicates fresh synthesis. This release could be evoked from many tissues by physiological, mechanical or pathological stimuli (Piper and Vane, 1971). Ferreira *et al.* (1976) concluded from *in vitro* studies on rabbit jejunum strips that PG release was proportional to the amount of manipulation of or damage to the tissue. Piper and Vane (1971) considered that distortion of the cell membrane caused by any stimulus could release PG. In our experiments, the demonstration of significantly higher levels of PG-like activity in the bladder washout fluid following pelvic nerve stimulation suggests that these values cannot be a consequence of the bladder washout process or of the surgical trauma.

Our experiments do not exclude the possibility of the presence of other types of PGs in the bladder effluent fluid, but the major biological active constituent appears to be PGE$_2$-like material. The specificity of the bioassay technique is well established for detection of PGs (Vane, 1969).

The only substances in concentrations of 1 to 20 ng/ml that can cause contraction of tissue strips in the presence of the combined antagonists were found to be prostaglandins of the E and F series (Ferreira and Vane, 1967). Gilmore *et al.* (1968) found that the rat stomach strip is most sensitive to the E series of prostaglandins. The detection of PG-like material in 8 out of 12 washouts collected from resting bladder, in our experiments, suggests continuous generation of PGs by the bladder. This finding is in accordance with *in vitro* studies on bladder strips and substantiates the hypothesis that PGs contribute to the tone of the bladder (Eckenfels and Vane, 1972; Bultitude *et al.*, 1976).

Significantly high levels of PGE$_2$-like activity were detected in the bladder fluid effluent following pelvic nerve stimulation. Similarly, cholinergic nerve stimulation was associated, in other animals, with PG release from the stomach (Coceani *et al.*, 1967) and the heart (Junstad and Wennmalm, 1974). These elevated levels of PGs are of particular significance in the bladder because it has been suggested that PGs are involved in the excitatory bladder transmission of many animal species (Choo and Mitchelson, 1977; Johns and Paton, 1977).

The source of the released PGE$_2$-like material detected in our experiments, whether released from

Table 3 Influence of Intravesical PGE$_2$ On Some Urodynamic Voiding Parameters*

	Control	*Intravesical PGE$_2$ dose (µg/ml saline)*					
	0.0	*0.03*	*0.1*	*0.3*	*1.0*	*3.0*	*P*‡
Maximum intravesical pres.	31.6	34.1 ± 0.6†	32.8 ± 1.2	32.8 ± 1.2	32.2 ± 1.1	33.4 ± 1.2	0.60
Urethral pres., resting	38.8	38.0 ± 0.7	41.1 ± 4.5	42.6 ± 5.8	33.3 ± 3.3	30.2 ± 3.9	0.19
Threshold micturition vol. (ml)	98.0	92.1 ± 2.4†	86.2 ± 5.7	86.2 ± 3.6†	78.0 ± 6.1†	74.4 ± 7.9†	0.03
Micturition cycle time (min)	12.2	12.2 ± 0.6	11.4 ± 0.4	10.2 ± 0.7 †	9.5 ± 0.7†	9.0 ± 0.7†	0.009

* Mean ± SEM values of 6 experiments. Pressure values are expressed in cmH_2O.

† A significant difference exists between values marked by † and their corresponding control as assessed by Student's t-test for paired values ($P < 0.05$).

‡ Associated probability for Fischer's analysis of variance; $P < 0.05$ is the level of significance.

the bladder mucosa or muscle, is difficult to establish. Bennett *et al.* (1968) found that 4 times more PGs could be extracted from the mucosa of the human stomach than from its submucosa, whereas only traces of PG-activity could be found in the muscle layer. Intravesically administered PGs, in this work, produced a significant dose-dependent drop of the threshold micturition volume and shortening of the time of the micturition cycles. These findings do not confirm the suggestion of Gilmore and Vane (1971) that locally released PG in the bladder could contribute to bladder accommodation. The mechanism of PGs' facilitatory influence on the micturition cycles is not clearly known. However, if PGs were absorbed through the bladder mucosa, they could exert an action on the detrusor muscle. PGE$_1$ was shown to be absorbed through the vaginal mucosa (Sandberg *et al.*, 1967). Blood samples collected from the vena cava during our intravesical PG experiments showed markedly elevated levels as compared to control values before PG administration, indicating PG absorption through the bladder mucosa (unpublished data). These absorbed PGs could probably affect micturition by 2 mechanisms:

(1) Prostaglandins may sensitise the stretch or tension receptors of the bladder wall so that reflex micturition is triggered at a lower threshold volume during bladder filling. Ferreira (1972) suggested a similar mechanism of action and concluded that PGE$_1$ or PGE$_2$ may be exerting their effect by sensitising the pain receptors at the site of inflammatory reaction.

(2) Prostaglandins may exert an inhibitory action on adrenergic transmission in the bladder. Prostaglandins of the E series are known to be potent inhibitors of norepinephrine release and adrenergic effector responses in a large number of tissues (Hedqvist, 1977). The functional implications of the interaction between the sympathetic and parasympathetic innervation of the dog urinary bladder (Raezer *et al.*, 1973) may involve, in part, the locally released PGs.

However, further experiments are needed to investigate the explanation of our observed results.

The influence of intravesically administered PG on the bladder capacity and micturition could raise the question of its therapeutic implications. Bultitude *et al.* (1976) showed that intravesical administration of PGE$_2$ reduced the maximum cystometric capacity and improved voiding in 14 of 21 patients having chronic urinary retention without distal obstruction.

The high intravesical doses needed to facilitate micturition, in our experiments, may preclude a physiological action of the relatively smaller amounts detected in the bladder effluent fluid under our experimental conditions. The latter could, however, be explained by the following facts:

(1) Bladder washout samples were done after voiding and bladder evacuation. We found that samples collected from voided fluid contained blood and other discharges, making the assay procedure a difficult one.

(2) We assayed PG-like activity on the rat stomach strips as E$_2$, so that prostaglandin F$_{2}\alpha$, if present, would have been underestimated.

(3) The bioassay results were not corrected for recovery. Using the same extraction technique as in the present work, we recovered 67.0 ± 8.4% of the original PGE$_2$ activity after extraction and evaporation (Rioux *et al.*, 1977).

(4) Renal PGs, in the urine, were excluded by preliminary urinary diversion.

In spite of these experimental conditions, our findings of the changes in micturition parameters in response to intravesically administered PGs, coupled with their possible release after micturition or after pelvic nerve stimulation, tend to suggest that PGs may play a role in micturition. However, our observations are preliminary and further experiments have to be performed to substantiate them.

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Clinical Experience with Intravesical Prostaglandin E_2

A Prospective Study of 36 Patients

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Summary—In a prospective study, intravesical prostaglandins were given to 36 patients who had urinary symptoms associated with a poorly functioning detrusor; 67% of these patients were found to be in chronic retention. Using standard urodynamic techniques, 72% showed objective evidence of an immediate improvement in detrusor function and there was prolonged therapeutic benefit in 39%. A prolonged response occurred only in patients who had an intact sacral reflex arc and urodynamic evidence of a pathologically enlarged bladder, and who did not have radiologically demonstrable outflow obstruction.

The use of intravesical prostaglandin to stimulate the detrusor was also found to be of value as a urodynamic technique for the investigation of the lower urinary tract.

In 1976, Bultitude *et al.* reported the results of their initial investigations into the effects of prostaglandin on the bladder both *in vitro* and *in vivo*. From their *in vitro* studies performed on detrusor muscle strips they established that (1) prostaglandins were produced by the detrusor, (2) prostaglandins E_2 and $F_{2\alpha}$ acted on strips of isolated detrusor to produce a dose-related contraction, (3) prostaglandin synthesis inhibitors caused loss of tone and spontaneous activity which could then be restored by exogenous prostaglandin, and (4) both prostaglandin and acetylcholine were required for the maintenance of normal tone and spontaneous activity. When intravesical prostaglandin was given to 21 females in chronic retention with apparently inactive detrusors, cystometry revealed a feeling of urgency at lower filling volumes and the return of a detrusor contraction with voiding. Subsequently their urinary symptoms improved and residual volumes were significantly reduced. Seven out of 21 cases failed to respond.

Since then we have continued to use intravesical prostaglandin (PGE_2) not only in females with chronic retention but also in the management of any patient whose urinary symptoms were considered to be primarily the result of impaired detrusor function. This paper reports the clinical and urodynamic findings in a prospective study of a further 36 patients treated with intravesical prostaglandin. The aim of the study was to determine the clinical usefulness of prostaglandin E_2 and to define more specifically the functional bladder abnormality that would respond to this method of treatment.

Patients and Methods

The patients consisted of 27 females and 9 males. The females were aged from 23 to 76 years (mean 47 years) and the males from 33 to 84 (mean 64 years). Their symptoms included frequency, recurrent urinary tract infection, hesitancy, voiding predominantly by abdominal straining, a feeling of incomplete bladder emptying, lower abdominal dragging pain not relieved by voiding, abdominal distension and incontinence. Four patients had such difficulty in passing urine that they suffered from infrequency of micturition, voiding only twice or less in 24 h. It was apparent that these patients could void satisfactorily only when their bladders were full to capacity. All but 4 of the 36 patients had a past medical history of an operation or illness which could have been instrumental in causing the underlying urological abnormality (Table 1).

All patients underwent routine urological assessment including excretion urography and cystoscopy to exclude organic pathology or endoscopic evidence of outflow obstruction. The specific urodynamic investigations included daily urine void-

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Table 1 Past History

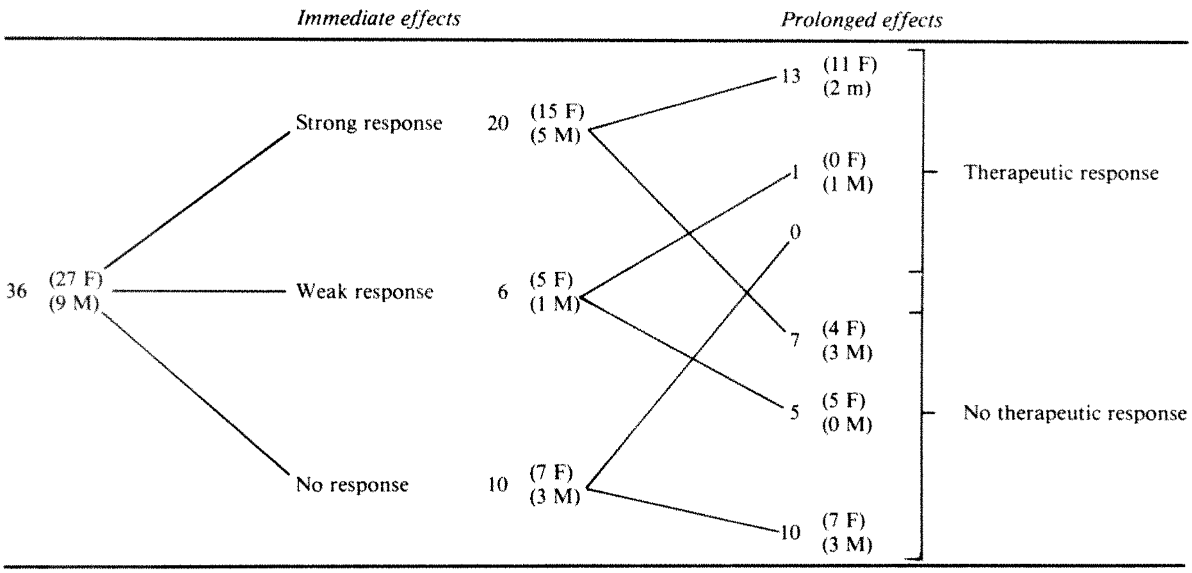
	Males	*Females*	*Total*
Hysterectomy	—	11	11
Prostatectomy	6	—	6
Anterior colporrhaphy	—	5	5
Spinal injury or disease	0	7	7
Other neurological disease	0	7	7
Major tranquillisers,	0	4	4
Proctocolectomy	1	0	1
Diabetes	0	1	1
Neurosyphilis	1	0	1
No relevant past history	1	3	4

ing volumes, residual urine measurements, filling and voiding cystometry, urine flow rates and videocystourethrography. Filling cystometry was performed with the patient in the supine position via a transurethral 12 FG Foley catheter using 35% diodone at 25°C as the filling medium, infusion being carried out at a continuous rate of 50 ml per min (medium fill cystometry). Simultaneous intravesical and intrarectal pressures were measured via 2 fluid-filled 6 FG plastic catheters (Portex) connected to physiological pressure transducers (Statham 23 db), the rectal pressure line being protected from blockage by covering its intrarectal opening with a plastic finger cot. These pressures and the subtracted detrusor pressure were recorded alongside a synchronous recording of the intravesical filling volume on an inkjet 8-channel chart recorder (Mingograf 81, Elema Schoenander). Special attention was paid to (*a*) the pressure filling gradient (henceforth referred to as bladder compliance and expressed in ml/cm H_2O), (*b*) the volume at which bladder sensation was first noticed and (*c*) the filling volume at which sensory discomfort occurred, which is defined as the conscious bladder capacity. The voiding phase of the cystometrogram was carried out in the sitting position for females and in the standing position for males. The maximum detrusor pressure (MDP) was measured and, if the pressure line was not extruded, the duration of the detrusor contraction. Recordings were also made of the peak flow rate (PFR), the mean flow rate (MFR) and the flow pattern by means of a von Garrelts type flowmeter. Simultaneous videocystourethrography was performed using an image intensifier (Siremobile, Siemans) and the video image displayed on a split screen monitor alongside a camera image of the chart recorder. These methods, definitions and units conform to the standards proposed by the International Continence Society (1976).

Indications, Administration and Method of Assessment

Patients were selected for treatment if they had voiding difficulties associated with either an apparently inactive (acontractile) detrusor at cystometry or a detrusor which was contracting but failed to produce complete emptying of the bladder at micturition in spite of the absence of

Table 2 Response to Intravesical Prostaglandin E_2



organic outflow obstruction. In this study, the level of residual urine alone was not used as a criterion for selection of patients for treatment. Of the 36 patients, 4 were in complete retention and required permanent catheterisation, 24 had residual urine volumes greater than 300 ml and were classified as having chronic retention, and 12 had residual volumes less than 300 ml. The latter included 4 patients with residual volumes less than 100 ml but this was achieved only with the assistance of abdominal straining during voiding.

Administration of intravesical prostaglandin was carried out after urethral catheterisation when the bladder was completely empty. The drug was supplied in an alcohol solution and had to be diluted with water or saline. For this study we used 1.5 mg of prostaglandin E_2 (Prostin E_2, Upjohn Ltd) diluted with 15 to 20 ml of 0.2% neomycin solution which was infused into the bladder, followed by a further 5 ml to flush the drug out of the catheter lumen; this was then left *in situ* for one hour.

The response to intravesical prostaglandin was assessed in 2 phases, the immediate effect and the prolonged effect. The former was determined by performing urodynamic studies immediately before treatment and repeating them in an identical manner one hour later. The recordings were then compared to see if there had been a reduction in detrusor compliance, bladder sensation onset volume, conscious bladder capacity or residual urine volume, or an increase in peak or mean flow rate. It was considered that prostaglandin had produced an immediate positive response if any one of these parameters showed an improvement by a factor of 40% or more. If only one parameter altered by more than 40%, the response was rated weakly positive, but if 2 or more parameters were altered, the response was rated strongly positive. A positive response was also recorded if prostaglandin led to a return of detrusor activity with voiding.

The evidence for a prolongation of effect was assessed by noting an improvement in the patient's symptoms, recording any reduction in the residual volume and in some cases by repeating the urodynamic evaluation.

Results

Of the 36 patients, 26 showed an immediate response to prostaglandin, 20 showed a 40% improvement in 2 or more parameters and so were rated strongly positive, and 6 showed a 40% improvement in only one parameter and were rated weakly positive. Fourteen of these went on to show evidence of prolonged beneficial effects and all but one had immediate responses which had been rated as strongly positive (Table 2). Of the 19 patients with acontractile detrusors, 13 showed an immediate response which was characterised in 11 patients by a return of detrusor activity with voiding. However, this activity persisted to produce normal voiding in only 7 patients (Table 3). Of the 12 patients who exhibited an immediate response but failed to show a prolonged response, 7 had strongly positive immediate responses and 5 had weakly positive immediate responses. None of the 10 who failed to exhibit an immediate response showed evidence of a delayed response.

A prolonged response was always associated with a considerable improvement in urinary symptoms. Frequency and incontinence associated with gross chronic retention were relieved and patients who complained of lower abdominal dragging

Table 3 Response to Intravesical Prostaglandin E_2 in Relation to Detrusor Activity

		Immediate effects		*Prolonged effects*	
Acontractile detrusors	19	No response	6	6	No therapeutic response
				6	
		Immediate response	13	7	Therapeutic response
Contracting detrusors	17	Immediate response	13	7	
				6	No therapeutic response
		No response	4	4	

Table 4 Case 1

	First sensation (ml)	*Capacity (ml)*	*Compliance (ml/cm H_2O)*	*Peak flow rate (ml/s)*	*Mean flow rate (ml/s)*	*Residual (ml)*
Before treatment	600	1000+	75*	25	6.25	640
After treatment	250	360	36*	26	8.18	0

* Total bladder pressure.

pain obtained complete relief even if they still failed to empty their bladders. Difficulty in voiding and the need for abdominal straining were either eliminated or became a very minor problem. Patients with infrequency of micturition returned to a normal pattern of voiding. In those who had prolonged symptomatic improvement, residual volumes varied between 80 and 2050 ml (mean 795 ml) before treatment and fell to levels of 0 to 550 ml (mean 253 ml) after treatment, an overall drop of 68%. Better responses were obtained in patients with residual volumes less than 1000 ml (in whom there was a mean reduction of 80%), whereas those with residual volumes greater than 1000 ml had a mean reduction of 61%. Of the 12 patients who were not in chronic retention (residual volume less than 300 ml), 4 had prolonged responses and showed a mean reduction in residual urine from 173 to 40 ml.

Case Reports

Case 1. J.B. Female aged 48 years. Developed acute retention after check cystoscopy for a previously endoscopically treated stage I carcinoma of the bladder. She was subsequently able to void but only with difficulty and largely by abdominal straining. Later she developed lower abdominal dragging pain and dribbling incontinence and was found to be in chronic retention with a residual urine of 600 ml. Cystometry revealed impaired bladder sensation, a capacity greater than 1000 ml and an acontractile detrusor, voiding being entirely by abdominal straining. Intravesical prostaglandin E_2 1.5 mg was given for one hour with dramatic results, including the return of a detrusor voiding contraction (Table 4). Incontinence, voiding by abdominal straining and lower abdominal dragging pain were all cured and the residual urine fell to 150 ml. A relapse of symptoms occurred at 4 weeks with similar urodynamic findings and a residual of 1200 ml, but she responded to a further dose of prostaglandin and remains symptom-free at 18 months.

Case 2. J.B. Female aged 47 years. Onset of difficulty in voiding in 1976. Anterior and posterior colporrhaphy performed for prolapse the same year did not have any immediate effect on her urinary symptoms. She was admitted in 1977 with hesitancy, frequency, voiding by abdominal straining, a poor stream and incomplete emptying which failed to improve following urethral dilatation. Initial residual urine was 80 ml but this was achieved only with the help of abdominal straining. Intravesical prostaglandin E_2 1.5 mg was given but only tolerated for half an hour because of severe urgency. Urodynamic studies revealed increased sensitivity and flow rates and a reduction in capacity and compliance. Initially her urinary symptoms completely disappeared but they started to return after 4 months, which correlated with a deterioration of the urodynamic findings performed after that time. Further improvement occurred at 9 months when prostaglandin treatment was repeated (Table 5).

Case 3. M.W. Female aged 45 years with a 4-year history of multiple sclerosis. Presented with a 4-month history of difficulty in passing urine, poor stream, voiding by abdominal straining and incomplete bladder emptying. She was found to have a residual of 200 ml, impaired bladder sensation, a capacity of over 1000 ml

Table 5 Case 2

	First sensation (ml)	*Capacity (ml)*	*Compliance (ml/cm H_2O)*	*Peak flow rate (ml/s)*	*Mean flow rate (ml/s)*	*Residual (ml)*
Before treatment	340	650	150	9	4.76	300
After treatment	180	500	28	13	6.08	50
At 1 month	190	470	67	18	9.71	0
At 4 months	460	630	125	10	5.71	30
At 9 months	550	770	—	16	5.80	240
After second treatment	240	500	—	20	8.57	30

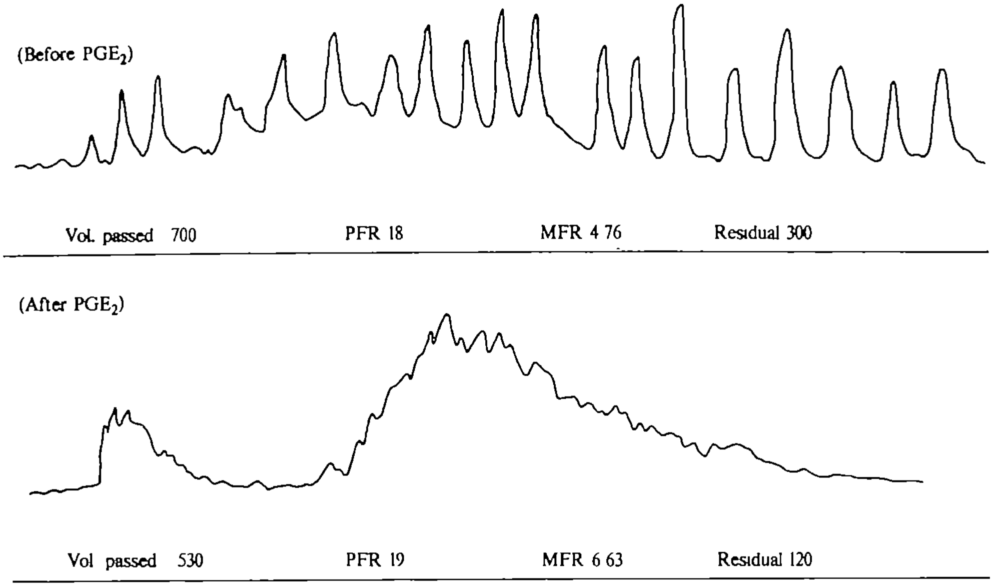


Fig. 1 Case 3: Flow pattern.

and an acontractile detrusor. Intravesical prostaglandin E_2 1.5 mg was given for one hour and this resulted in decreased detrusor compliance, marked urgency at 650 ml and voiding by a normal detrusor contraction with a dramatic change in flow pattern (Fig. 1). At the repeat study, owing to the improved flow rate produced by prostaglandin, it was possible to exclude any functional outflow obstruction by videocystourethrography. The patient's symptoms resolved except for very occasional difficulty in voiding and the residual volumes were reduced to less than 50 ml. A relapse occurred at 3 months but this responded to further treatment with prostaglandin.

Case 4. S.M. Female aged 23 years with a history of fits following viral meningitis in 1975. In 1977 she developed incontinence, voiding by abdominal straining and reduced frequency which culminated in urinary retention with residual volumes of 1500 to 2000 ml. She was then able to pass urine while taking cholinergic drugs but she continued to have reduced frequency and elevated residual urine volumes between 200 and 650 ml. Urodynamic studies performed while the patient was taking bethanecol 50 mg qds showed a capacity of 950 ml, a detrusor compliance of 260 ml/cm H_2O and a maximum detrusor voiding pressure of 24 cm H_2O. Intravesical prostaglandin E_2 1.5 mg was given for one hour, resulting in a lowered capacity of 650 ml, a detrusor compliance of 110 ml/cm H_2O, improved flow rates and an increase in detrusor pressure of 34 cm H_2O followed by a massive after-contraction of 70 cm H_2O (Figs. 2a and b). The infrequency of voiding was changed to a normal diurnal pattern and her residual urine has remained less than 100 ml.

Case 5. A.H. Female aged 44 years who had an abdominal hysterectomy in 1976 for menorrhagia, following which she developed progressive diurnal frequency. On admission in 1977 she was voiding 3 to 4 times per hour, felt unable to empty her bladder and complained of mild stress incontinence with a full bladder. Cystoscopy revealed mild trabeculation; urethral dilatation was ineffective. Urodynamic studies revealed an initial residual volume of 350 ml, impaired sensation and a capacity of 750 ml at cystometry. Voiding occurred totally by abdominal straining with an intermittent flow rate and a residual volume of 430 ml. Intravesical prostaglandin E_2 1.5 mg was given for one hour, resulting in a reduced capacity of 500 ml, voiding by a sustained detrusor contraction and a dramatic increase in flow rate with a change in flow pattern and complete emptying of the bladder (Fig. 3). Screening with an improved flow rate made it possible to detect intermittent spastic closure of the midurethra during voiding in spite of a sustained detrusor contraction. The symptoms recurred after 3 days and further prostaglandins were ineffective. Follow-up studies have demonstrated a normally contracting detrusor but there is persistent midurethral narrowing compatible with detrusor sphincter dyssynergia.

Case 6. M.S. Female aged 36 years. Developed urinary retention 2 days and again one year after hysterectomy for fibroids aged 30 years and again after laminectomy for a prolapsed disc aged 33 years. Presented with a history of hesitancy, voiding by abdominal straining, frequency, lower abdominal dragging pain and recurrent urinary tract infections. Excretion urography and renal function were normal but cystoscopy revealed

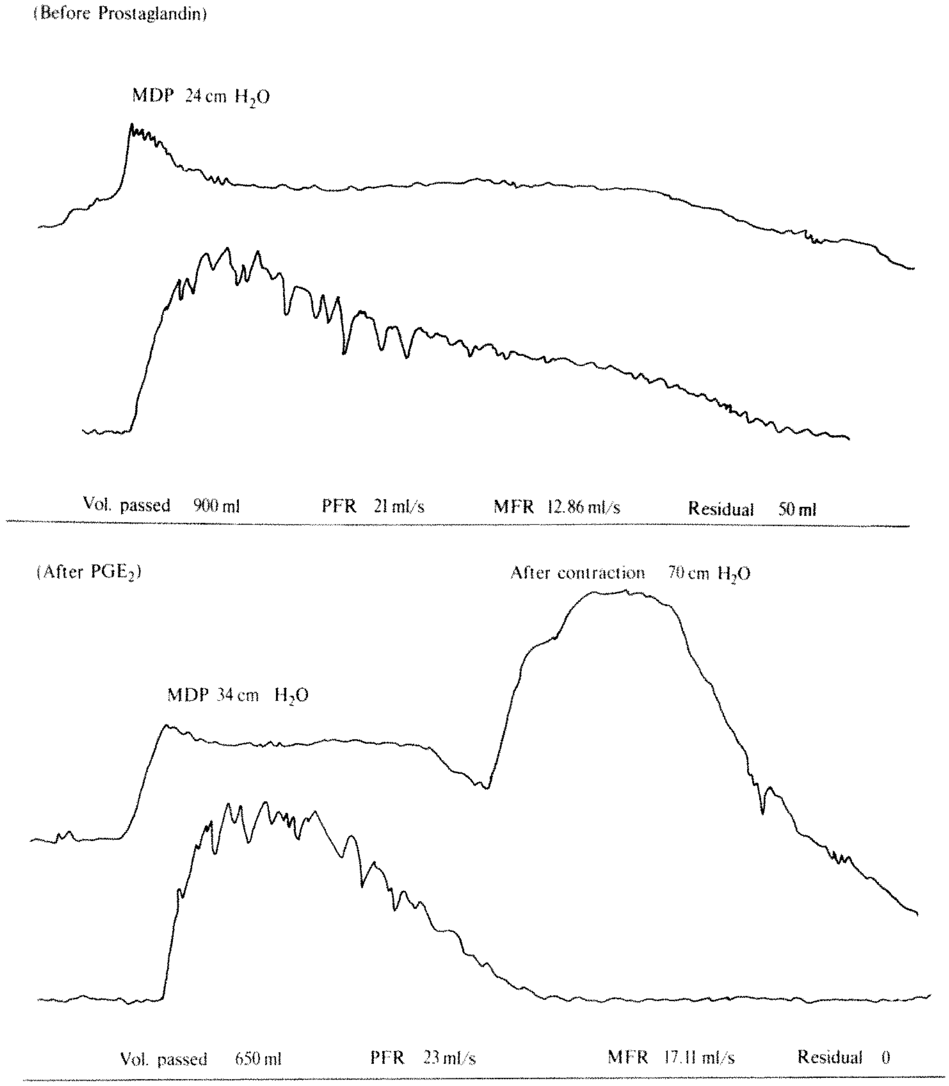


Fig. 2 (a) Case 4: On Bethanecol 50 mg qds. Upper trace: Subtracted detrusor pressure; Lower trace: Flow pattern. (b) Case 4: On Bethanecol 50 mg qds + Prostaglandin E_2 1.5 mg intravesically. Upper trace: Subtracted detrusor pressure; Lower trace: Flow pattern.

marked trabeculation, urethral narrowing and a residual urine of 1400 ml. Her frequency and hesitancy were considerably improved by urethral dilatation but the residual volume persisted at levels of 1100 to 1200 ml and she still complained of lower abdominal dragging pain. Cystometrogram revealed a hypercompliant detrusor, impaired sensation and a capacity of 1370 ml. Intravesical prostaglandin E_2 1.5 mg was given for one hour, resulting in a reduction in sensation onset volume from 1120 to 410 ml, capacity from 1370 to 510 ml and compliance from 500 to 83 ml/cm H_2O. The patient received 2 further doses of intravesical prostaglandin at weekly intervals, each resulting in a further improvement (Table 6). The patient is symptom-free but has a residual urine of 580 ml 6 months after her last dose of prostaglandin.

Case 7. H.C. Male aged 84. Admitted with a 3-month history of severe prostatism associated with incontinence and lower abdominal swelling. He was found to be in chronic retention with a blood urea of 15.2 mmol/l and minimal upper tract dilatation on excretion urography. Following transurethral resection of a benign prostate, the patient went back into painless chronic retention with a residual of 2000 ml. Attempts to produce voiding by cholinergic drugs were unsuccessful. Intravesical prostaglandin E_2 1.5 mg was given on 2 consecutive days with a dramatic reduction in compliance, bladder

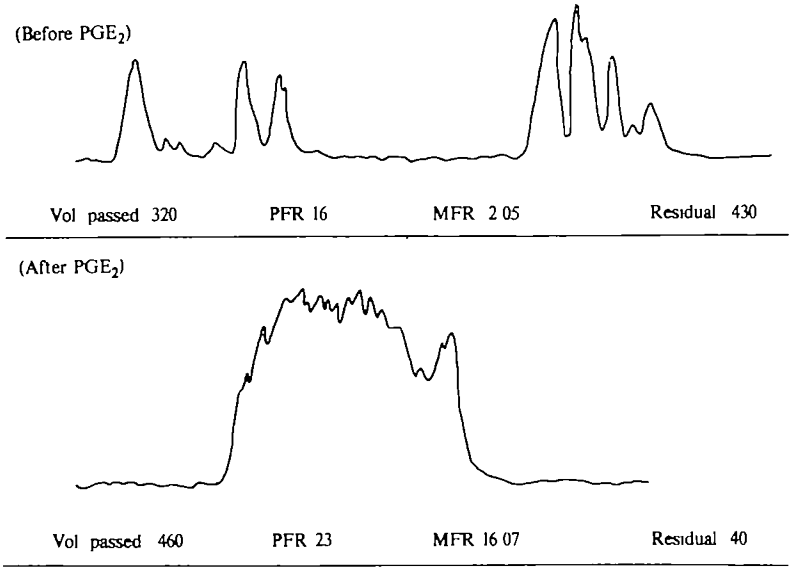


Fig. 3 Case 5: Flow pattern.

sensation onset volume and capacity after each dose. Despite this, however, the patient was unable to void until repeat cholinergic stimulation was instigated; this, in combination with prostaglandin, resulted in satisfactory voiding. Residual urine was 270 ml at follow-up 2 months later (Table 7).

Analysis of the urodynamic findings in these patients revealed certain differences between those who responded and those who failed to respond to intravesical prostaglandin. Four patients were found to have lower motor neurone lesions; all of them had acontractile detrusors and all failed to show even the slightest improvement in any of the measured parameters. Two patients had primary sensory neurone lesions, one due to neurosyphilis and the other to a diabetic autonomic neuropathy; both showed strong immediate responses but in neither were the effects prolonged. Five other patients who showed no prolonged response were discovered to have outflow obstruction unrevealed at the initial endoscopy; in one case this was due to recurrence of a posterior urethral stricture and in the other 4 cases it was due to functional obstruction caused by detrusor sphincter dyssynergia; in 3 of these this was associated with multiple sclerosis. A further 7 patients failing to show prolonged benefit were found to have a normal filling phase to their cystometrogram, whereas all those who did have a prolonged response had an abnormal filling phase at cystometry as shown by increased detrusor compliance (hypotonia), impaired bladder sensation (bladder sensation onset volume greater than 300 ml) and a conscious bladder capacity greater than 600 ml. When comparing the patients who had contracting detrusors with those who had acontractile detrusors, the number of patients who responded both in the immediate phase and the prolonged phase was not significantly different. After excluding the 4 patients with definite

Table 6 Case 6

Day		*Volume passed (ml)*	*PFR (ml/s)*	*Residual (ml)*	*First sensation (ml)*	*Capacity (ml)*	*Compliance (ml/cm H_2O)*
0	Before first treatment	280	14	1150	1120	1370	500
0	After first treatment	—	—	—	410	510	83
7	Before second treatment	200	12	880	—	—	—
7	After second treatment	—	—	—	520	600	56
14	Before third treatment	250	13	570	—	—	—
14	After third treatment	—	—	—	450	580	48
28	After third treatment	—	—	480	—	—	—

Table 7 Case 7

	First sensation (ml)	*Capacity (ml)*	*Compliance (ml/cm H_2O)*
Before treatment	Absent	2000 +	83*
After first treatment	500	700	42*
After second treatment	200	320	9*

* Total bladder pressure.

lower motor neurone lesions, it was found that the response rate for contracting bladders was 76% in the immediate phase and 41% in the prolonged phase, and in the case of the acontractile bladders the response rates were 87% and 47% respectively. There was also no overall difference between the 2 groups in the degree of response. However, when the pattern of micturition changed from that of voiding by abdominal straining to one of voiding by means of a detrusor contraction, the improvement observed was much more dramatic.

In the group of patients who had previously undergone gynaecological surgery were 13 who had undergone 17 operations; these included 11 hysterectomies, 5 anterior colporrhaphies and 1 Marshall Marchetti procedure. All but one patient showed an immediate response to prostaglandin, 9 strongly positive and 3 weakly positive. Six patients who obtained prolonged therapeutic benefit had strongly positive immediate responses. Of the remaining 7 patients, one had outflow obstruction associated with multiple sclerosis and 3 were in the group with a normal filling phase to their cystometrogram. These 3 had in fact responded dramatically to intravesical prostaglandins on a previous occasion, when their symptoms had been associated with chronic retention and abnormal filling cystometry. The remaining 3 patients without prolonged responses had chronic retention and an abnormal filling phase at cystometry, but it was interesting that in these patients the urinary symptoms dated directly from the time of pelvic surgery, whereas all those who showed a prolonged response in this study or as a result of previous prostaglandin therapy had a symptom-free period between their pelvic operation and the onset of symptoms.

The number of male patients who received intravesical prostaglandin was only 9, and 6 of them had voiding difficulties following prostatectomy for benign prostatic hypertrophy. Therapeutic responses were obtained in only 3 patients, all of whom had persistent post-operative chronic retention secondary to hypotonic acontractile detrusors. Attempts to restore adequate voiding by cholinergic stimulation or intravesical prostaglandin alone proved unsuccessful, but cholinergic stimulation combined with intravesical prostaglandin resulted in satisfactory relief of chronic retention in each case. However, it must be stated that we have found from previous experience that intravesical prostaglandin alone can be effective in restoring normal voiding in patients who remain in gross retention following prostatectomy and this has occurred in 3 patients who were not part of this study.

Discussion

The immediate response of the bladder to stimulation by intravesical prostaglandin can be extremely dramatic, as has been demonstrated by the case reports presented in this paper. Not only has prostaglandin been shown to increase bladder sensitivity, detrusor tone and detrusor contractility, but it can also restore detrusor activity in a bladder that has lost its ability to contract in response to the normal stimulus of distension. However, the presence of an intact sacral reflex arc appears to be a prerequisite for any form of response.

In the assessment of the immediate response, measurement of the peak flow rate was relatively unhelpful, since it was found that some patients could achieve equally good peak flow rates by abdominal straining as by a detrusor contraction and, in this respect, the mean flow rate was more reliable. The maximum detrusor pressure and the duration of the detrusor contraction could not always be recorded because of the rapid expulsion of the transurethral pressure line on some occasions, but case 4 demonstrates the effect of prostaglandin on the amplitude and duration of the detrusor voiding contraction in a bladder already under the influence of cholinergic stimulation.

In some patients the dose of intravesical prostaglandin was varied to ascertain the optimum treatment regime. It was found that larger doses did not necessarily have a greater effect and it seemed more important to ensure that the bladder was completely empty and that the drug was not rapidly diluted by a diuresis from the kidneys; thus fluid restriction before treatment was desirable. In this study, the drug was left *in situ* for one hour if tolerated; longer periods were tried but did not afford any additional benefit. On the other hand, consecutive treatments produced an increasing response in 3 patients who started with residual volumes of over 1000 ml. Side effects from therapy were mild and included a burning sensation in the perineum at the time of infusion down the catheter and increasing urgency during the instillation period. More troublesome side effects included malaise, abdominal pain, facial flushing, dry mouth, headaches, diplopia, nausea, giddiness and spontaneous defaecation, but these occurred in only 3 patients, 2 of whom were given larger doses, and one exhibited a reaction to even the smallest dose.

Continuation of the response for a prolonged period produced lasting benefit in 39% of the patients. However, it was found that this occurred only if a significant response to prostaglandin could be demonstrated in the immediate phase, if there was urodynamic evidence of a pathologically enlarged bladder and if there was no radiologically demonstrable outflow obstruction.

Urodynamic studies were performed before and after administration of intravesical prostaglandin primarily to assess the immediate response, but it appears that this response is useful in predicting the likelihood of a prolonged effect. A weak response in the immediate phase suggests either ineffective administration of the drug or the improbability of a prolonged therapeutic response. The use of intravesical prostaglandin has also proved valuable as a technique for urodynamic evaluation. Many of these patients during their preliminary investigation were unable to void sufficiently well to permit satisfactory radiological assessment of their lower urinary tract. However, if an immediate response to prostaglandin led to the restoration of detrusor activity or improvement in voiding, it was then possible to identify or exclude any functional outflow obstruction. It was also found that patients with complete lower motor neurone lesions failed to demonstrate even a minimal change in any of the measured parameters following intravesical prostaglandin, whereas the other patients with overdistended bladders and abnormal cystometry showed some response, even though it did not always reach a significant level. This basic difference in response may be a useful pharmacological method of determining the presence of an intact sacral reflex arc in patients with overdistended bladders, but this requires further evaluation.

Other workers have also described similar actions of prostaglandins on detrusor muscle strips *in vitro* (Abrams and Feneley, 1976; Andersson *et al.*, 1977). Ghoneim *et al.* (1976) detected an increase in prostaglandin E_2 in the inferior vena cava of dogs in response to vesical distension which coincided with a fall in urethral pressure. The role of prostaglandin E_2 as a neurotransmitter for this response was suggested on the basis that it was mimicked by prostaglandin E_2 and blocked by indomethacin, a potent prostaglandin synthesis inhibitor. Stanton and Cardozo (1978) assessed the use of prostaglandin on urodynamically normal bladders to relieve acute retention after colposuspension operations and found that the retention was unrelieved, but no urodynamic assessment of the detrusor after administration of prostaglandin was made.

The effect of prostaglandin E_2 on the poorly functioning detrusor, and especially its surprising long-term effect, is again confirmed in this series. Increased sensation on bladder filling and the return or enhancement of detrusor motor activity were observed. Prolonged changes were achieved in 3 patients only by a combination of prostaglandin and cholinergic agents; in a fourth patient, prostaglandin further improved the function of a detrusor which was already under cholinergic stimulation. These clinical observations confirm the findings of our previous muscle strip experiments, but further studies are needed to elucidate the site of action of prostaglandin E_2 in the bladder.

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The Management of Urgency and Frequency of Micturition

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Summary—The historical pattern of frequency and urgency of micturition is outlined and their role as the prime motivator of detrusor instability discussed. Thirty female patients were analysed; provocative cystometry was performed in 22 of them. Their management is reviewed and a programme of out-patient treatment submitted.

Urgency of micturition is usually described as a dominant symptom of detrusor instability. The author maintains, however, that urgency has also a much more serious connotation in that voluntary frequency may well be an initiating factor in detrusor instability rather than simply a symptomatic consequence of it. The historical pattern of detrusor dysfunction and its clinical manifestations support such a hypothesis and further endorsement of the instigatory role of frequency is well exemplified by bladder training. The basic concept of such training is to focus the patient's attention on the adoption of a graduated negative response to the urgency desire to micturate, and to overcome by instruction her abnormal voiding routine. Therapy is thereby directed to the control of the urgency/frequency symptoms by the voluntary suppression of the abnormal micturition habit, rather than by directing treatment towards the detrusor muscle itself. Once urinary control is established stability may follow (Frewen, 1979).

If self-induced frequency of urgency is acceptable as an inaugural factor in the unstable bladder, it follows that energetic treatment of this factor in its early phase should eventually diminish detrusor instability.

Patients and Procedures

An analysis was made of 30 consecutive patients who presented with urgency and/or frequency of micturition, 10 of whom also complained of a variable degree of urgency incontinence. Their ages ranged from 15 to 65 years (mean 39 years). The duration of symptoms was from 1½ to 14 years. Nocturia (voiding twice or more times at night) was present in 16 cases, and one patient had intermittent enuresis. Frequency of micturition alone was present in 9 patients who had diurnal voiding intervals of between 30 and 60 min.

A detailed micturition history was obtained from all patients, with special emphasis on the origin of symptoms and their relation, if any, to childhood voiding habits, either diurnal or nocturnal. A search was made for an emotive aetiology. Abdominal, vaginal or rectal examinations were carried out as a routine, and a mid-stream specimen of urine sent for culture and analysis. Provocative cystometry was performed in 22 cases. Cystoscopy had previously been done on 5 patients, but as they all showed no abnormality, cystoscopy was not performed in any of the remaining cases, particularly as their satisfactory progress did not warrant it.

Findings

An emotive aetiology was manifest in only 20% of cases. The urine culture was sterile in all cases. Only 8 patients of the 22 showed bladder instability.

Management

Patients with urgency or frequency of micturition do not need hospitalisation and may be managed effectively by out-patient care. The aim of management was to increase the bladder capacity day by day by prolonging the intervals between micturition.

The deleterious effects on bladder function of frequent and urgent voiding and the relevance of

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bladder training in overcoming such symptoms were pointed out to each patient.

Each patient was given a voiding chart and instructed to record the exact times of voiding throughout the day and also at night if there was associated nocturia. On the first day the patient then had a complete record of her voiding times and intervals. From then onwards the primary objective was to increase these intervals gradually and to record them in writing until the desired 4-hourly interval was achieved. Surveillance was continued at monthly intervals for a period of 3 months.

Results

At the end of 2 months most patients had reached the desired target of 3 to 4-hourly frequency (Fig.).

The criterion of cure was that within a period of 3 months from the onset of treatment the patients were free from all urinary symptoms and that their voiding intervals were maintained at 3 or more hours.

At the conclusion of 12 weeks' treatment 24 of the 30 patients achieved the above objectives and were subjectively free from their urinary symptoms. In 13 of the 24 patients a 3 to 4-hour micturition interval was obtained at the end of 4 weeks' therapy, but they still had some degree of diurnal urgency. With one exception nocturia was the first symptom to disappear. All of the 9 patients with frequency of micturition alone, especially those in the younger group, responded well.

The objective results were not so gratifying, since stability was restored in only 3 of the 8 unstable bladder patients after completing 3 months' therapy. This was not unexpected, however, as the disappearance of urinary symptoms may well ante-date the return to normal cystometry by a period of 2 or 4 months.

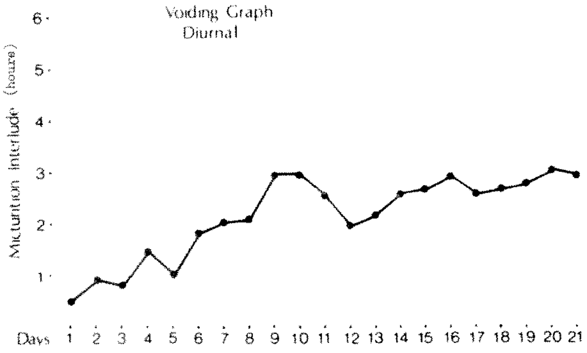

Fig. Female aged 29 years with a 7-year history of diurnal frequency at 30-min intervals. After 21 days of voiding recording the graph illustrates the improvement to a 3-h micturition interlude.

Five of the 6 failures had residual urgency and a micturition interval of less than 3 h, and one of them had postural leakage of urine. The sixth patient refused to record her voiding pattern and showed little symptomatic improvement.

Discussion

The historical background of the urgency syndrome does not support the assumption that urgency is the effect of detrusor instability. On the contrary, it strongly suggests that urgency of micturition may well be the prime motivator of detrusor dysfunction as a result of its detrimental action on bladder storage and emptying. This concept is supported by the findings that in only 8 of the 22 cases was it possible to demonstrate an unstable bladder, and the fact that half of the patients were aged between 15 and 30 years and the average duration of symptoms in that group was less than 2 years.

It is relevant to note that patients with stable bladders responded much more readily to bladder training than those with unstable bladders. This is not surprising, since the former patients were in an earlier phase of the disorder and therefore reacted more readily to appropriate therapy. The interval between the onset of urgency and the onset of bladder instability is a highly individual characteristic and is difficult to quantify.

Although unusual, it is recognised that detrusor instability may be present without associated urgency of micturition. However, in such circumstances frequency of micturition is almost always apparent and it may be that as a result of frequent voidings the delicate physiological balance of storage and emptying is disturbed. Unstable detrusor function may well follow, because the bladder is just as likely to react unfavourably to frequent emptying as to excessive storage. Any dislocation of the physiological symbiosis of emptying and storage may foreshadow undesirable sequelae in detrusor behaviour. It is illogical to accept that prolonged storage may produce detrusor hypotonia, and not to accept that frequent voiding may equally precipitate abnormal detrusor activity.

With the associated augmentation of bladder capacity the urgency desire gradually abates and disappears.

Supportive therapy to diminish the induced bladder instability by the use of anticholinergic drugs is usually helpful, especially when there is associated nocturia. Patients of a nervous disposition will require the additional aid of mild antidepressant or sedative drugs. However, the intelligent patient who has a clear appreciation of the issues involved will not necessarily need any drug therapy. Certainly in the younger age group Pro-Banthine in doses of 30 mg 3 or 4 times a day is helpful; in the elderly, however, Cetiprin 200 mg given at 8-hourly intervals is preferable. If the patient has associated nocturia or enuresis the last dose of Cetiprin at night should be increased to 400 mg.

Prolongation of the recorded voiding intervals, however small, is the key to success provided that there is a graduated continual progression.

Bladder training will often need to commence in infancy and childhood and, above all, in school. Acceptance of the "weak bladder" diagnosis is a gesture of despair and an almost certain invitation for the patient to develop uninhibited detrusor activity in later life. Urgency or frequency of micturition may, of course, develop spontaneously in any age group and for a variety of reasons, and it may well then become an established habit. The habit develops into an addiction until it is accepted by the patient as an inconvenient routine. The acceptance of such a voiding pattern will not only be injurious to the patient but also to her children, who will be likely to develop the urgency/frequency ritual by the simple process of mimicry. Perpetuating circumstances are thus established and in future years detrusor instability and urinary incontinence will almost inevitably follow.

The author maintains that by appropriate bladder training of the urgency/frequency syndrome the unstable bladder may well become an infrequent disorder.

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Scanning Electron Microscopy in the Study of Normal, Inflamed and Neoplastic Human Urothelium

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Summary—Seventy-two samples of human urothelium have been examined by scanning electron microscopy (SEM) and the appearances compared with those of conventional light microscopy. Six main SEM cell types were recognised. None was diagnostic of malignancy; in particular, the presence of surface pleomorphic microvilli was not pathognomonic. However, the relation of the SEM appearance to malignancy and the accepted histological grades and clinical stages of malignancy was such as to warrant further examination.

In recent years, transmission electron microscopy and scanning electron microscopy have been used to study the structure of normal and neoplastic human urothelium in greater detail. Routine light microscopy is of considerable diagnostic assistance but of limited prognostic value, especially in the case of well differentiated non-invasive tumours of the bladder (Cooper *et al.*, 1969; Lessing, 1978).

In work with rats given the carcinogenic agent methyl nitrosurea, Hicks (1976) has shown characteristic cell surface appearances in the bladder on scanning electron microscopy. The development of pleomorphic microvilli was shown to be a sign of irreversible malignant change proceeding to invasion of the bladder wall. This appearance was present before signs of malignancy were seen on light microscopy. Studies in man have shown similarities to the animal model (Newman and Hicks, 1977; Hodges, 1978; Tannenbaum *et al.*, 1978). Since September 1978 we have employed SEM in the routine practice of our Urology and Pathology Departments to determine if these findings could be substantiated with larger numbers of patients and thus be of value in the clinical management of early bladder cancer.

Material and Methods

Tissue Samples

Specimens of urothelium were obtained during routine investigation and treatment of patients with prostatism, infective cystitis, the frequency/dysuria syndrome, urothelial tumours past or present, calculus disease, idiopathic pelviureteric obstruction and renal cell carcinoma. Most specimens were obtained from the bladder by endoscopic diathermy resection or by biopsy forceps, in sterile water. Specimens from ureter and 4 non-malignant bladders were obtained at open operation. Specimens were of 4 types:

(1) Urothelial carcinoma.

(2) Macroscopically normal urothelium with urothelial cancer present elsewhere in the urinary tract.

(3) Macroscopically normal urothelium with a past history of urothelial cancer.

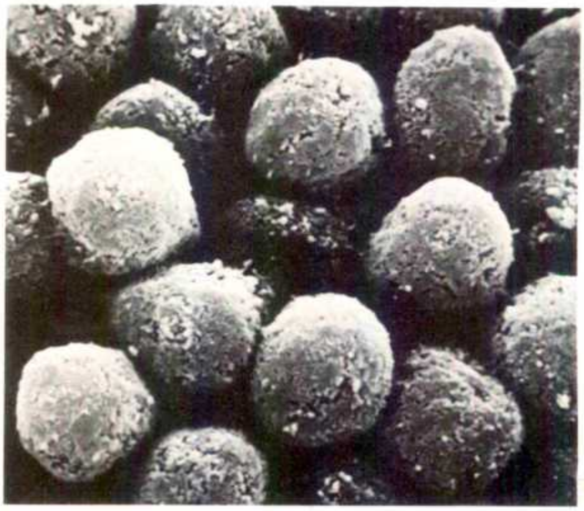

Fig. 1 SEM cell Type 1. Small, rounded cells with very few surface features (× 5900).

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(4) Specimens with no known associated malignancy.

Patients with inflammation or infection were not excluded, but there were no specimens from patients who had had recent radiotherapy. Adjacent samples were sent for routine histology and for SEM.

Specimen Preparation

For histology, specimens were fixed in 10% phosphate buffered formaldehyde and stained with haematoxylin and eosin.

Samples for SEM were fixed and/or stored in 3% glutaraldehyde in 0.1 M sodium cacodylate buffer at 4°C for periods between 24 h and 1 month. Dehydration was in graded concentrations of acetone. Specimens were critical point dried in a Polaron E 3000 apparatus using liquid carbon dioxide, mounted on stubs with double-sided adhesive tape, care being taken that the urothelial surface was uppermost, and coated with approximately 100 Å of gold in an Emscope SEMcoat sputter coating apparatus. Specimens thus prepared were examined in a Jeol JSM T20 Scanning Electron Microscope using an accelerating voltage of 12.5 kV.

Clinical Data

Note was taken of the cystoscopic appearance, bimanual examination, urine culture, blood urea and intravenous urogram. Histological interpretation was by one pathologist (ARM). Tumours were classified according to the UICC TNM system (Wallace *et al.*, 1975) and WHO tumour grading (Mostofi *et al.*, 1973; Koss, 1975).

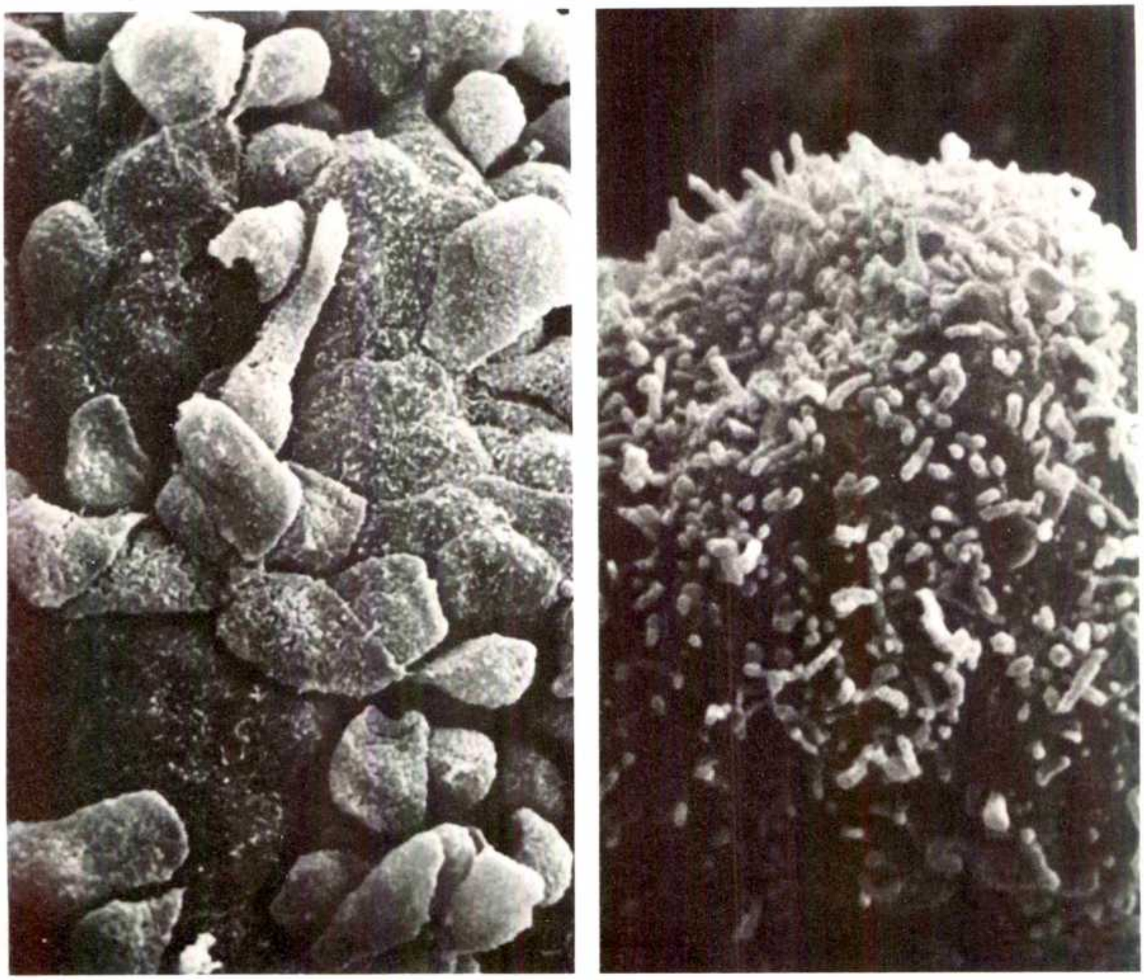
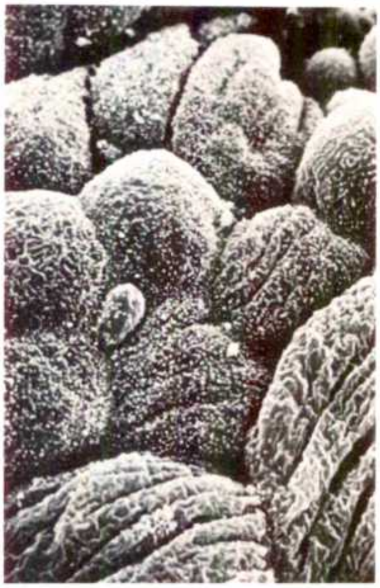
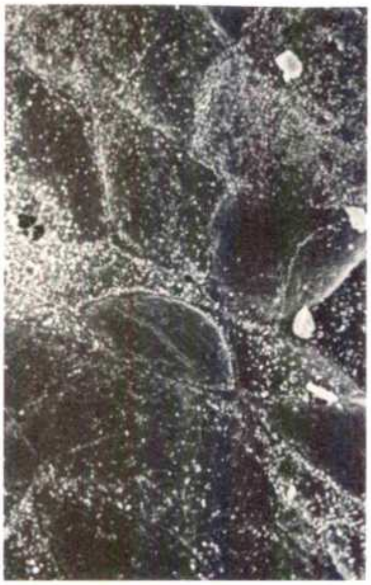


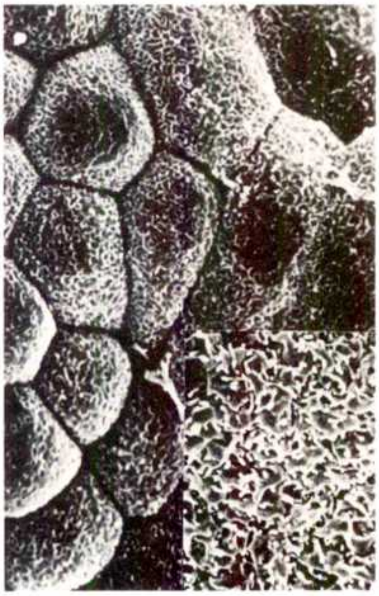
Fig. 2 SEM cell Type 2. (a) (left) An irregular surface with pleomorphic microvilli on many cells (× 1600). (b) (right) A higher power view of one of these cells showing the pleomorphic microvilli (× 15,700).

SEM Characterisation

Photographs were taken of all specimens at SEM examination with magnifications of 35-100, 1500 and 5000-10,000. The photographs were examined, and by comparing size, shape, surface appearance and degree of attachment to the surrounding cells, cells were classified into 6 main types (Figs. 1-6). Where there was a range in cell size the average







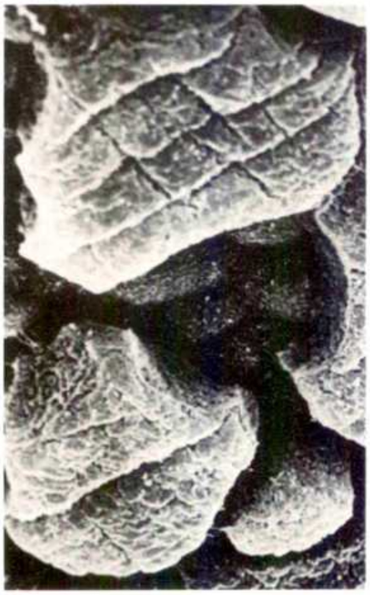


Fig. 3 (top left) In the centre can be seen SEM Type 3 cells with scattered short microvilli (×3150). In this example of urothelium, reported histologically as hyperplasia, a number of other cell types are also present: Type 1 in top right-hand corner. Type 5 centre right, and the large Type 6 cells, bottom.

Fig. 4 (top right) SEM cell Type 4. Smooth cells with varying numbers of microvilli. The microvilli tend to be concentrated at the margins of the cells (×2400).

Fig. 5 (bottom left) SEM cell Type 5. Cells have surface ridges (×2600). Inset: another example of one cell with a very complex surface (×5500).

Fig. 6 (bottom right) SEM cell Type 6. Large cells with ridges and folds. Note tight junctions with shrinkage artifact. In the centre a large cell has been lost, revealing the much smaller, deeper cells (×2400).

size was obtained from the mean of the average sizes from all of the specimens showing that type of cell.

Type 1 Round smooth cells (Fig. 1). These cells were small, approximately 7-8 μm in diameter; some were isolated, some attached to the basement membrane by cytoplasmic processes. They had poor cell-to-cell contact and very few microvilli.

Type 2 Cells with evenly distributed pleomorphic microvilli (Figs. 2a and b). Some of these cells had long cytoplasmic processes with poor cell-to-cell contact; others were flatter with good cell-to-cell contact. Cell size was approximately 11 to 12 μm. All had uniformly distributed pleomorphic microvilli.

Type 3 Cells with evenly distributed short globules (Fig. 3). The globules could also be termed short regular microvilli. Cell-to-cell contact was good but the globules usually obscured the actual junctions. Cell size was approximately 14 μm.

Type 4 Smooth surface cells or cells with short or pleomorphic microvilli concentrated at the margins (Fig. 4). This was the most heterogeneous group, cell size varying between 8.9 and 23.4 μm (average 14.3 μm). They formed good cell-to-cell contact, often with a distinct "seam" at the junction. Microvilli were limited to the cell periphery and in areas where there were no microvilli the surface was featureless.

Type 5 Cells with complex ridge formation (Fig. 5). This group consisted of rounded cells, showing complex surface patterns and ridges suggesting fusion on microvilli, and large flat cells with complex leaf-like folds sometimes surmounted by short globular microvilli. Occasionally the folds were much flatter although still in evidence again with short microvilli. It is possible that the prominence of the folds depended on degree of distension. Cell size was between 17 and 26 μm (average 22 μm).

Type 6 Large cells with folds and ridges on the surface (Fig. 6). The difference from Type 5 was the increased cell size and greater complexity of surface ridges. However, the features were never as exuberant as Type 5. Cell size was approximately 30 μm.

Specimens were graded into one of the above groups depending (*a*) on the presence or absence of each cell type and (*b*) on the *predominant* cell type seen. The predominance of a certain cell type was determined from the approximate percentage area covered by that type in the medium power photomicrograph compared to the other cell types present. Often different cell types were seen on the same specimen, suggesting, but not proving, progression through the SEM spectrum or possible cell maturation (*e.g.* Fig. 3).

Results

Seventy-two specimens were examined from 67 patients. Ages ranged from 18 to 84 years, most being between 60 and 70 years; 51 were male and 16 female. There were 36 bladder and 1 renal pelvis transitional cell tumours, 26 non-neoplastic bladder specimens and 9 samples of non-neoplastic upper urinary tract urothelium.

Table 1 shows the relationship between the SEM predominant cell type and histological diagnosis. Types 2 to 4 were significantly more common than Types 5 and 6 in tumour specimens (27/37; $0.01 > P > 0.001$), while Types 5 and 6 were seen more commonly than Types 2 to 4 in non-neoplastic urothelium (23/35; $P < 0.001$). The only sig-

Table 1 Relationship Between SEM Predominant Cell Type and Histological Diagnosis: Number of Specimens in Each Group

SEM predominant cell type	*Tumour*	*Normal bladder*	*Normal ureter*	*Inflammation*	*Hyperplasia*	*Total*
6	1	1	2	1		5
5	5	6	5	4	4	24
4	13	2	1	3	2	21
3	5	1		1		7
2	9	1		1		11
1	4					4
Total	37	11	8	10	6	72

Table 2 Presence of Type 2 Cells (Cells With Pleomorphic Microvilli)

	Tumour	*Non tumour bearing urothelium*		*Total*
		Tumour in past/ elsewhere	*No previous history of urothelial tumour*	
SEM Type 2 cell present	19	5	5	29
Type 2 absent	18	11	14	43
Total	37	16	19	72

nificant incidence of a single cell type in neoplastic or non-neoplastic tissue was of Type 5 which was more common in non-neoplastic specimens ($P < 0.001$). The statistical method used was the chi-squared test with Yates' correction. Type 2 cells occurred as the predominant cell type in only 9 out of 37 tumours.

Table 2 shows the association of malignancy with the presence rather than the predominance of Type 2 cells (*i.e.* cells with scattered pleomorphic microvilli). Nineteen out of 37 tumour specimens contained Type 2 cells compared with 5 out of 19 non-neoplastic controls. Five out of 16 non-neoplastic specimens with an association of malignancy in the past or elsewhere in the urinary tract showed Type 2 cells. Thus cells with pleomorphic microvilli were found in only 51% of proven tumours and also occurred in 26% of histologically normal tissue with no known association of malignancy. These differing incidences are not statistically significant (χ^2 with Yates' correction).

Figure 7 compares the SEM predominant cell type with the histological tumour grade. Grade III, poorly differentiated tumours were of SEM Types 1 to 4; Grade III, moderately differentiated tumours were of SEM Types 2 to 5 and Grade I, well differentiated tumours were of SEM Types 2, 5 and 6. There were only 5 Grade III stage T3 tumours and 4 of these consisted entirely of Type 1 cells; the other had Type 3 as its predominant cell type.

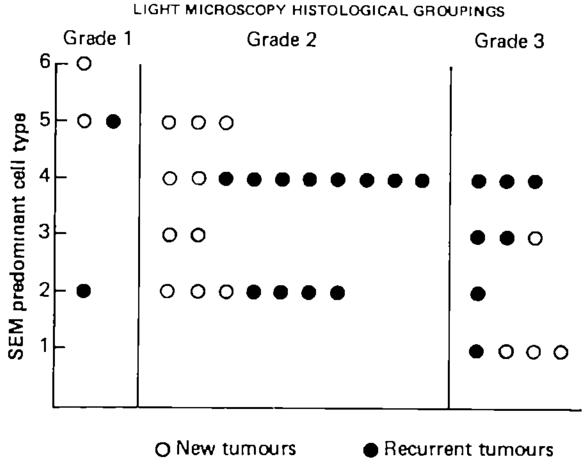


Fig. 7 Light microscopy grade and SEM predominant cell type of each tumour specimen.

In the whole series 16 specimens were new tumours and 21 were recurrent tumours (Fig. 7). Of the new tumours, 5 had predominant cell Types 5 and 6; 7 moderately differentiated tumours had Types 2 and 4; one poorly differentiated tumour had Type 2, while 3 Grade III infiltrating tumours had Type 1. Of the 21 recurrent tumours, cell Type 5 was predominant in only one and this was a well differentiated, non-invasive tumour. The remainder, of varying histological grades, were all Types 1, 2, 3 or 4.

Discussion

The most complete description of bladder cell surface appearance so far is that of Hodges in normal rat and non-malignant human bladder (Hodges *et al.*, 1977; Hodges, 1978). This classification is based on the concept of a 3-layered urothelium comprising basal cells, intermediate cells and superficial cells. Hodges described basal and immature intermediate cells as having relatively smooth surfaces, while maturing intermediate cells developed short microvilli which seemed to amalgamate and form chain-like processes. These became more and more complex leaf-like folds until full differentiation was reached with the complex ridges and folds of superficial cells. The latter were caused by thick plaques of the plasma membrane interspersed with thinner areas as seen by transmission electron microscopy.

It can be seen that Hodges' basal cell corresponds to our Type 1, her maturing intermediate cell to our Types 3 and 5 and the superficial cell to our Type 6. Our Types 2 and 4 were seen only in malignant and hyperplastic tissue respectively in her series. Kjaergaard *et al.* (1977) drew attention to the similarity between well differentiated tumour cells and the intermediate cells of normal urothelium, and between poorly differentiated tumour cells and the cells in the basal area of the non-neoplastic epithelium.

On the basis of these observations the Type 6 cell is more mature than Type 1 and the different cell types may be interpreted as showing progressive maturation. However, at present this can be regarded as no more than an hypothesis and the results of our study have been analysed according to the predominant cell type rather than the most "mature" cell present.

In this study there is no one cell surface appearance that indicates malignancy (Tables 1 and 2). This is in agreement with the study of 9 patients by Kjaergaard *et al.* (1977). In contrast, in a study of 35 patients with bladder cancer, Nelson *et al.* (1979) reported the obvious presence of pleomorphic microvilli on tumour cells regardless of the grade of malignancy and detected no microvilli in biopsies from 27 men without malignancy suffering from prostatic obstruction. Infected patients were excluded. Merk *et al.* (1977) in 10 patients also noted that all Grade I and II urothelial carcinomas had pleomorphic microvilli on SEM examination. While approximately half of our tumours showed microvilli, we found that the cells of Grade III stage T3 tumours were smooth and devoid of pleomorphic microvilli and some Grade I-II papillary T1 tumours lacked microvilli, having ridges similar to the normal urothelium. This concurs with the findings of Fulker *et al.* (1971) and Hodges (1978). Tannenbaum *et al.* (1978) also described uniform microvilli in tumours but the more undifferentiated the tumour (that is Grade II) the greater was the loss of surface microvilli in many cells.

In inflamed or hypertrophic urothelium the predominant cell types were 4 and 5 and in none did smooth round cells (Type 1) predominate.

These differences in results may be due to sampling errors which may be clarified by the analysis of larger numbers of patients. Alternatively, differences in specimen collection and preparation may be responsible. Barber and Burkholder (1975) showed that the incidence of microvilli on lymphocytes diminished with decreasing osmolality of the fixatives used. Our use of sterile water for cystoscopy compared with the isotonic irrigating medium of Nelson *et al.* (1979) may thus be significant. However, our biopsies obtained at open operation did not differ from those collected after water irrigation and Kjaergaard *et al.* (1977) had employed isotonic saline solution. All of the specimens in Tannenbaum's series were obtained at open operation. The most obvious difference in specimen preparation was the use of osmium tetroxide as a post-fixative by Kjaergaard *et al.* (1977), Merk *et al.* (1977) and by Nelson *et al.* (1979). This fixative was not used in the present study, nor was it employed by Fulker *et al.* (1971) or Tannenbaum *et al.* (1978). Osmium tetroxide confers more osmotic stability on the cells after glutaraldehyde fixation, but there is no reason to suppose that surface structures such as microvilli can be altered after the use of glutaraldehyde.

Although we have not been able to confirm that a specific SEM appearance is diagnostic of malignancy or pre-malignancy, certain trends are apparent which deserve further investigation. Cells with microvilli occurred as the predominant cell types more commonly in neoplastic tissue, while cells with ridges and folds occurred more commonly in non-neoplastic tissue. Almost all recurrent tumours had microvilli compared with new tumours that displayed the whole range of SEM cell types; thus it is possible that the presence of microvilli will indicate a greater tendency to tumour recurrence.

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Total and SHBG-bound Testosterone and 5α-Dihydrotestosterone Serum Concentrations in Normal Elderly Men and Patients with Benign Prostatic Hypertrophy Before and After Removal of the Adenoma

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Summary—Serum testosterone, 5α-dihydrotestosterone and their binding by sex hormone binding globulin (SHBG) were quantified in 10 patients with prostatic hypertrophy, before and after retropubic prostatectomy, and in an age-matched control group. Testosterone was significantly higher in the sera of the BPH patients. The SHBG-bound testosterone and 5α-dihydrotestosterone were identical in both groups, but the fraction of testosterone and 5α-dihydrotestosterone not bound to SHBG was higher in the group with BPH. Therefore patients with prostatic hypertrophy are exposed to increased androgen action.

Prostatectomy did not lead to significant changes in serum testosterone, 5α-dihydrotestosterone or their binding to SHBG.

The aetiology of prostatic hypertrophy remains unclear, but it is known to be an age-dependent and androgen-dependent disease (Geller, 1974). There seems to be, however, little or no difference in serum concentrations of total testosterone between normal men and patients with benign prostatic hypertrophy (Vermeulen and De Sy, 1976; Ghanadian *et al.*, 1977), although a tendency to elevated levels of testosterone in older BPH patients has been observed (Vermeulen and De Sy, 1976; Hammond *et al.*, 1978). The concentrations of 5α-dihydrotestosterone in blood have been shown to be elevated in patients with this disease (Horton *et al.*, 1975; Vermeulen and De Sy, 1976; Ghanadian *et al.*, 1977; Hammond *et al.*, 1978), and 5α-dihydrotestosterone has also been shown to be secreted by the hypertrophic prostate (Mahoudeau *et al.*, 1974).

The free, unbound fraction of circulating sex steroids may be a very important component of androgen action in man (Vermeulen *et al.*, 1969; Vermeulen and Verdonck, 1972; Anderson, 1974). It is possible that SHBG regulates the supply of the hormone to the target tissue and thereby controls its biological action (Lasnitzki and Franklin, 1975), and the percentage of unbound testosterone exhibits an inverse-logarithmic relationship with SHBG binding capacity (Anderson *et al.*, 1975). Therefore changes in unbound androgen might be reflected by larger changes in SHBG-bound androgens.

In this study total and SHBG-bound testosterone and 5α-dihydrotestosterone were measured in peripheral venous blood samples taken from BPH patients before and after retropubic prostatectomy and in a group of normal elderly men. The purpose was to evaluate the possible changes in these parameters in order to increase our understanding of the endocrine milieu of patients with benign prostatic hypertrophy.

Patients and Methods

Ten patients with benign prostatic hypertrophy (prostate adenoma weight over 50 g) volunteered for this study. The mean age of these patients was 68 years; none had previously been treated with any hormonal preparations, nor were they observed to have any additional endocrine disease. The control group consisted of 10 patients, mean age 71 years, who had no history of prostatic disease or other endocrine disorders and who showed no evidence of hypertrophy after rectal

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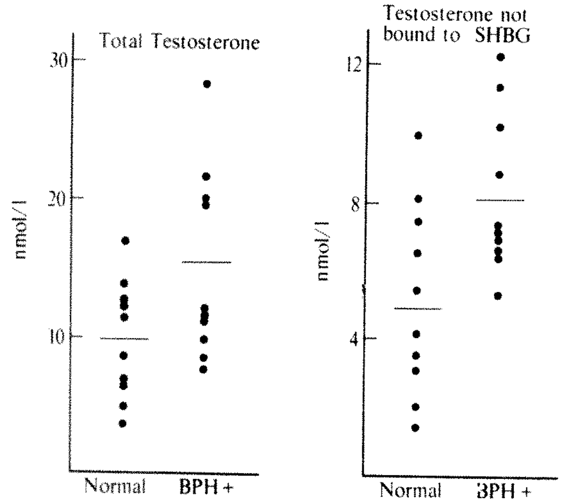

Fig. 1 Total (left panel) and testosterone not bound to SHBG (right panel) in peripheral serum of the normal subjects and the patients with benign prostatic hypertrophy (BPH+). The horizontal bars represent mean concentrations.

palpation of their prostates. Blood samples were taken between 8.30 and 9.30 a.m. from BPH patients one day before and one month after a retropubic prostatectomy, and similarly from control subjects. Serum in all cases was obtained after clotting and centrifugation and stored at −20°C until the analyses were performed.

Plasma testosterone and 5α-dihydrotestosterone were estimated after solvent extraction and chromatographic purification of extracts on Lipidex-5000™ (hydroxyalkoxypropyl Sephadex from Packard-Becker, B. V., Chemical Operations, Groningen, The Netherlands) prior to the radioimmunoassay of both steroids using specific antisera. The methodology employed was very similar to that described recently from this laboratory (Hammond *et al.*, 1977b and c). The sensitivity, precision, accuracy and specificity of the respective radioimmunoassays have been previously defined in detail (Jänne *et al.*, 1974; Apter *et al.*, 1976). Water blanks (1 ml) and low, medium and high control samples were included in each batch of samples as quality controls. The percentual amount of specifically SHBG-bound testosterone and 5α-dihydrotestosterone was estimated by the differential dissociation technique (Horst *et al.*, 1974). Calculation of bound testosterone and 5α-dihydrotestosterone was determined after correction for dilution by plotting the disintegrations per min against time on a semi-logarithmic scale. The linear part of the dissociation curve was extrapolated to time zero (t_0) and the specifically bound steroid calculated as a percentage of the total radioactivity present at t_0. The precision of the method was determined using 5 aliquots of 2 plasma samples. The mean intra-assay coefficient of variation was 6.2% for testosterone and 4.0% for 5α-dihydrotestosterone.

Statistics

Groups were compared using an independent 2-tailed Student's t-test.

Results

In the present series, the serum concentration of total testosterone in the peripheral veins of BPH patients before prostatectomy was higher ($P < 0.05$) than in the control group. In contrast to this, there was no significant difference in the concentrations of total 5α-dihydrotestosterone. The mean serum concentrations (±SD) of these 2 hormones in normal control and BPH groups were: testosterone 9.62 nmol/l ± 4.24 (for individual values, see Fig. 1) and 15.02 nmol/l ± 6.93 (Fig. 1); 5α-dihydrotestosterone: 1.45 nmol/l ± 0.66 and 2.00 nmol/l ± 0.70 (Fig. 2), respectively.

The mean values of the percentage binding of testosterone and 5α-dihydrotestosterone to SHBG in the control group were: 48 ± 12% and 70 ± 17%, and in the BPH group: 42 ± 17% and 64 ± 17%, respectively. There was no significant difference

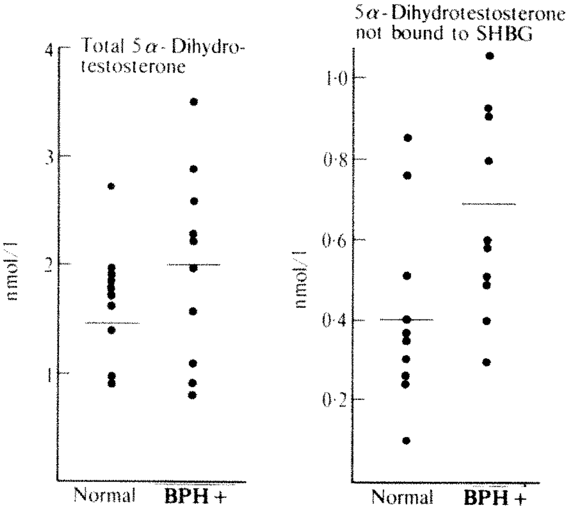

Fig. 2 Total (left panel) and 5α-dihydrotestosterone not bound to SHBG (right panel) in peripheral serum of the normal subjects and of the patients with benign prostatic hypertrophy (BPH+). The horizontal bars represent mean concentrations.

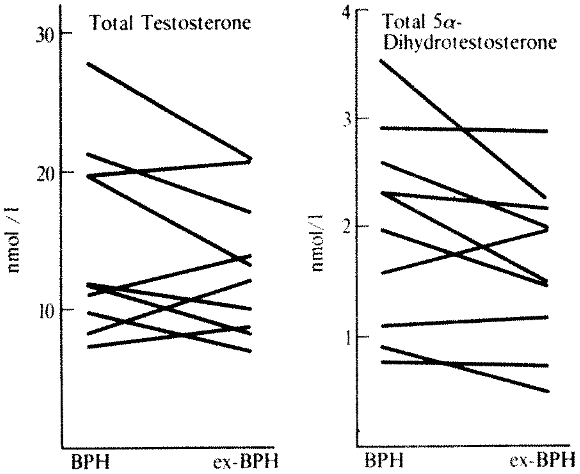

Fig. 3 Serum total testosterone (left panel) and 5α-dihydrotestosterone (right panel) before (BPH) and after (ex-BPH) retropubic prostatectomy.

between these groups in the binding of these 2 steroids to SHBG. However, the unbound and albumin-bound testosterone ($P < 0.02$) and 5α-dihydrotestosterone ($P < 0.05$) were lower in the control group than in the BPH group. The mean concentrations of unbound and albumin-bound testosterone in the control and BPH groups were as follows: 5.20 nmol/l ± 2.59 and 8.12 nmol/l ± 2.40 (Fig. 1), respectively, and those of the same fraction of 5α-dihydrotestosterone were 0.41 nmol/l ± 0.24 and 0.66 nmol/l ± 0.23 (Fig. 2), respectively.

The peripheral serum concentrations of the total testosterone and 5α-dihydrotestosterone before and one month after prostatectomy are presented in Figure 3. After removal of the adenoma there was no change in the mean concentrations of serum testosterone and 5α-dihydrotestosterone. The same is true for the levels of unbound and albumin-bound fractions of these steroids (Fig. 4).

Discussion

The results of the present study support the view that prostatic hypertrophy is associated with increased circulating androgen concentrations. Total serum testosterone was found to be elevated when compared with an age-matched group of normal subjects, thus supporting previous findings from this laboratory (Hammond *et al.*, 1978). Serum 5α-dihydrotestosterone was slightly but not significantly higher in the present BPH group. It is well established that the circulating concentrations of 5α-dihydrotestosterone are elevated in patients with BPH, but this has not always been observed, possibly because of the large variation in its concentrations in peripheral serum and partly because of difficulties in establishing an age-matched control group free of BPH.

Although 5α-dihydrotestosterone is produced by the hyperplastic prostate (Mahoudeau *et al.*, 1974; Lukkarinen *et al.*, 1980), the importance of this secretion for the levels of circulating 5α-dihydrotestosterone seems to be minimal, because there was no change in its serum concentration one month following removal of the BPH adenoma.

Recently, the binding capacity of SHBG in sera from BPH patients was reported not to differ from normal controls (Dennis *et al.*, 1977). In this study, the percentage binding of testosterone and 5α-dihydrotestosterone to SHBG did not differ when the group of BPH patients was compared with a group of control subjects. However, the amounts of testosterone and 5α-dihydrotestosterone not bound by SHBG were significantly higher in the patients with BPH. Therefore the patients with this disease are exposed to increased androgen action. This may explain the low serum luteinising hormone (LH) level in patients with BPH (Hammond *et al.*, 1977a) and the suppression of pituitary LH and thyroid-stimulating hormone (TSH) responses to luteinising hormone releasing hormone (LHRH) and thyrotropin releasing hormone (TRH) associated with this disease (Hammond *et al.*, 1979).

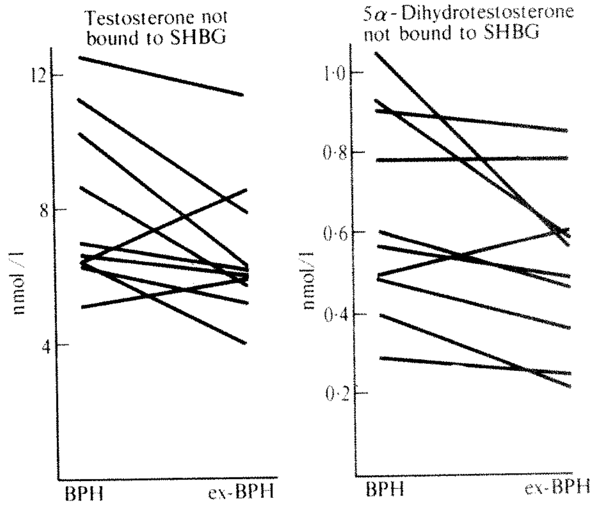

Fig. 4 Testosterone (left panel) and 5α-dihydrotestosterone (right panel) not bound to SHBG before (BPH) and after (ex-BPH) retropubic prostatectomy.

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Macrophages in Prostatic Fluid

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Summary—Non-specific esterase staining has been found useful in the detection of macrophages in prostatic fluid (PF).

In the early stage of acute prostatitis most of the leucocytes in a smear of PF took up the stain, suggesting the dominant participation of macrophages in the inflammatory area in this stage of the disease. In chronic prostatitis, only a few leucocytes took up the stain. In female acute cystitis, none of the large numbers of leucocytes exhibited staining at any stage of the disease. The reason for this is still to be determined.

Frozen sections of prostatic tissue from patients with chronic prostatitis revealed similar cells around the acini and these appeared to be the source of the macrophages which appeared in the PF.

Diagnosis and assessment on follow-up of cases of chronic prostatitis remain difficult even with the examination of the PF by leucocyte count (Farman and McDonald, 1959) and culture (Meares and Stamey, 1968; Drach, 1974), and examination of the seminal fluid by culture (Schnierstein, 1964; Mobley, 1975), immunoglobulin level (Nishimura *et al.*, 1977a), immunoelectrophoresis (Nishimura *et al.*, 1977b) and prostatic biopsy (Drach, 1974). Of these various examinations, leucocyte count of the PF is most widely used in daily practice because of its simplicity, but its significance remains controversial (Mobley, 1974).

In an attempt to evaluate the leucocytosis in the PF, we studied the macrophage subpopulation of leucocytes in PF, detecting them by non-specific esterase staining.

Frozen sections of prostatic tissue from cases of prostatitis or benign prostatic hyperplasia (BPH) were also stained in a similar manner to detect the presence of macrophages and their location.

Materials and Methods

Smears of prostatic fluid were obtained by prostatic massage from acute and chronic prostatitis patients. Acute prostatitis was diagnosed in patients with an acute onset of symptoms and a markedly tender prostate with or without a positive bacterial culture from the PF. Chronic prostatitis patients had at least a 6-month history of mild symptoms such as low back pain, perineal or groin discomfort, frequency of micturition and a feeling of incomplete bladder emptying, and had more than 20 leucocytes per high power field (HPF) in the PF. Urine specimens were obtained from women with acute cystitis who had pyuria.

Prostatic tissue from cases of chronic prostatitis

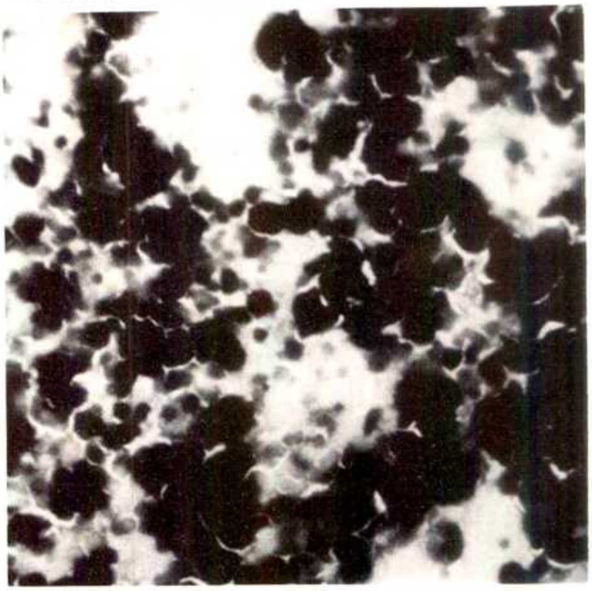

Fig. 1 Smear of prostatic fluid at early stage of acute prostatitis (× 100).

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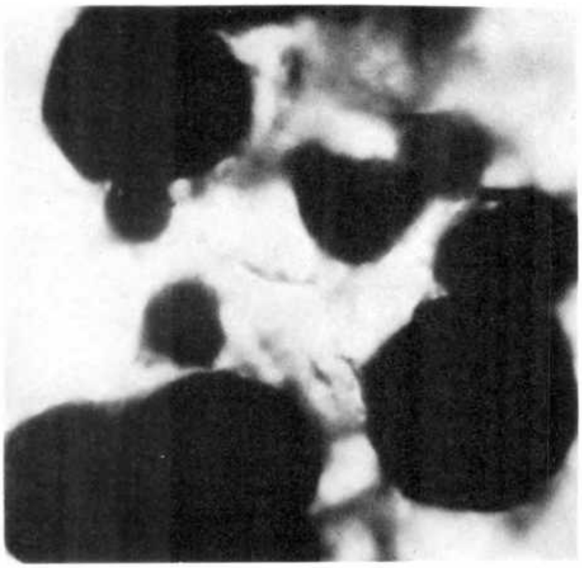

Fig. 2 Higher magnification (×600) of section shown in Figure 1.

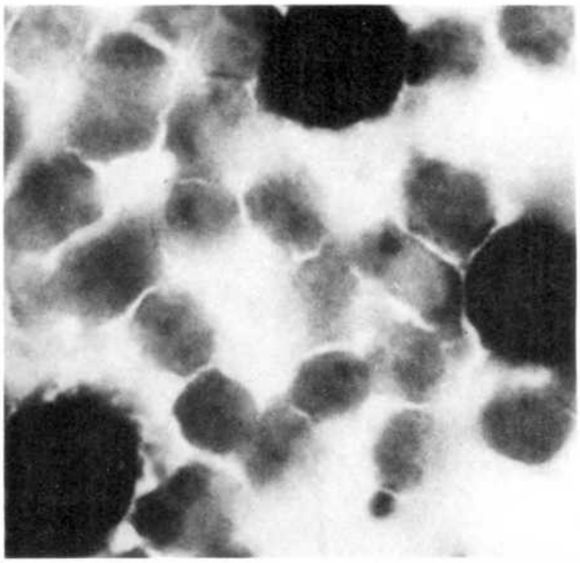

Fig. 4 Higher magnification (×600) of section shown in Figure 3.

or BPH was obtained by needle biopsy or open prostatectomy respectively and specimens were immediately frozen and sectioned at 4 microns in a cryostat.

Peritoneal exudate cells (PEC) were prepared from guinea pigs (female Hartley strain, weight 250 to 300 g) by injecting mineral oil intraperitoneally, followed by washing of peritoneal cavities with Eagles' minimal essential medium 3 days later.

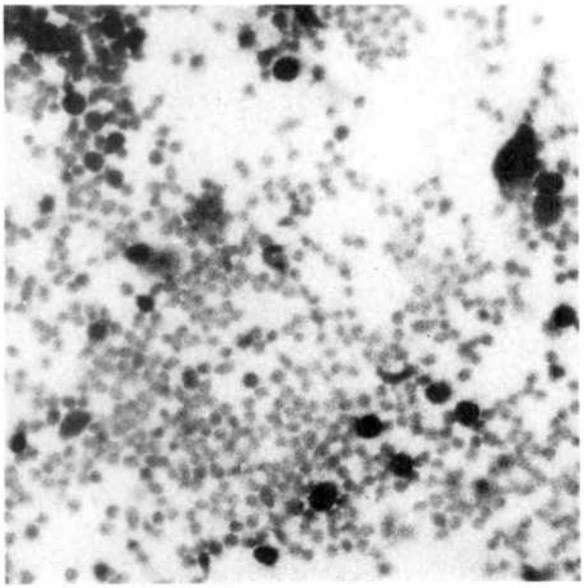

Fig. 3 Smear of prostatic fluid from chronic prostatitis patient (×100).

Staining for non-specific esterase and counterstain were performed according to the method of Yam *et al.* (1971). Enzyme activity for non-specific esterase was seen as dark red granules. Enzyme activity was inhibited by sodium fluoride (NaF) (Li *et al.*, 1973).

Results

Smears of PF in the early stage of acute prostatitis showed large clumps of cells intensely stained for non-specific esterase (Figs. 1 and 2).

Smears of PF from patients with chronic prostatitis showed only a few stained cells amongst the otherwise unstained leucocyte population (Figs. 3 and 4).

These intensely stained cells were very similar in colouration and shape to guinea pig PEC (Fig. 5). From this and the previous reports of other investigators (Yam *et al.*, 1971; Mueller *et al.*, 1975; Horwitz *et al.*, 1977; Knowles *et al.*, 1978), we have regarded these stained cells as macrophages. In defining a macrophage we have adopted the nomenclature of van Furth *et al.* (1975) who used the term "mononuclear phagocyte system". Therefore, in the present study, macrophages include both monocytes and histiocytes either in the prostatic tissue or fluid. Staining of frozen sections of prostatic tissue from patients with chronic prostatitis showed similar cells around the acini (Figs. 6 and 7). In addition to these cells, some elements of the stroma of the prostate, espe-

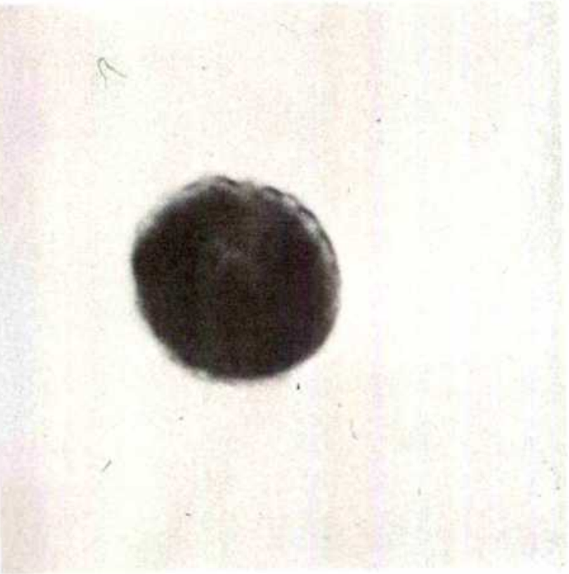

Fig. 5 Smear of guinea pig PEC (×1000).

cially the smooth muscle, also took up the stain but only to a lesser extent (Fig. 8).

Leucocytes in the urinary sediment from female patients with acute cystitis remained unstained (Figs. 9 and 10).

The enzyme activity was completely inhibited by NaF.

Discussion

The leucocyte count of the prostatic fluid is commonly used in the diagnosis of prostatitis. However, there is considerable controversy regarding the upper limit of normal, and some investigators discount its significance (Leader, 1958).

In the present study we have investigated the presence of macrophages, a subpopulation of leucocytes, in an attempt to solve this problem.

Macrophages can be detected by adhesion of modified erythrocytes, phagocytosis of latex beads or staining for a cytoplasmic esterase. In our preliminary experiment, staining for a cytoplasmic esterase was found to be the most appropriate method of detection of macrophages in the urinary tract.

Cytochemical identification of monocytes, in this case staining for a cytoplasmic esterase, was first described by Yam *et al.* (1971), and an increasing number of articles in recent years have described the usefulness of non-specific acid alpha-naphthyl acetate esterase staining not only for the demonstration of monocytes, but also for the differentiation of T and B lymphocytes (Mueller *et al.*, 1975; Horwitz *et al.*, 1977; Knowles *et al.*, 1978). However, we were unable to find any previous research in the urological literature which used this method for the detection of macrophages in the urinary tract.

In the present study, the first attempt to demonstrate macrophages in the prostatic fluid

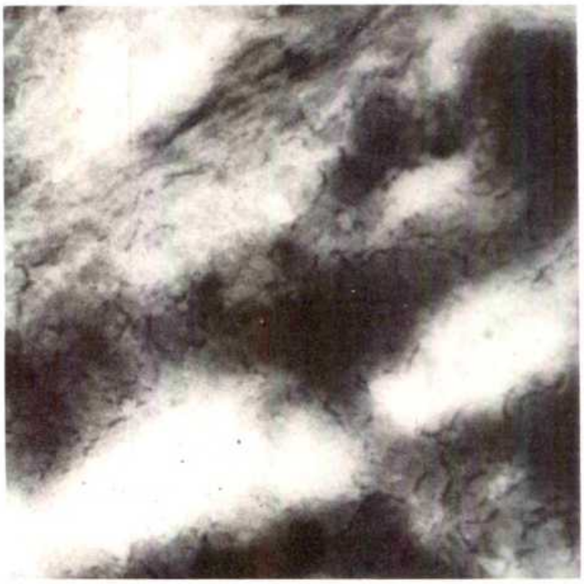

Fig. 6 Frozen section of prostatic tissue from patient with chronic prostatitis showing macrophages around acini (×100).

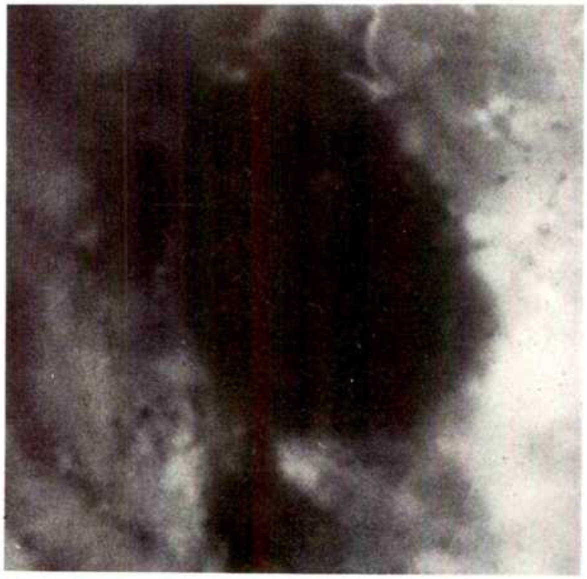

Fig. 7 Higher magnification (×1000) of section shown in Figure 6.

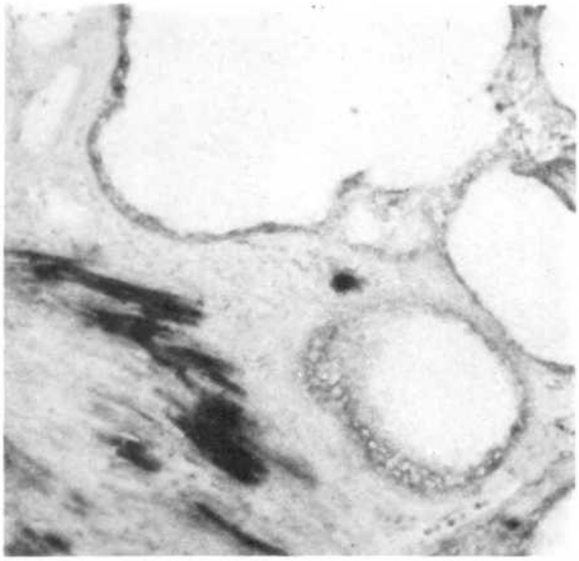

Fig. 8 Frozen section of prostatic tissue from BPH patient illustrating light staining of smooth muscle (×60).

by staining for a cytoplasmic esterase is reported. Different patterns of staining were observed in acute prostatitis compared with chronic prostatitis and female acute cystitis, whilst smears made without specific staining showed only leucocytosis without differential features.

In the early stages of acute prostatitis, most of the leucocytes in the PF were intensely stained, which suggests a predominance of macrophages.

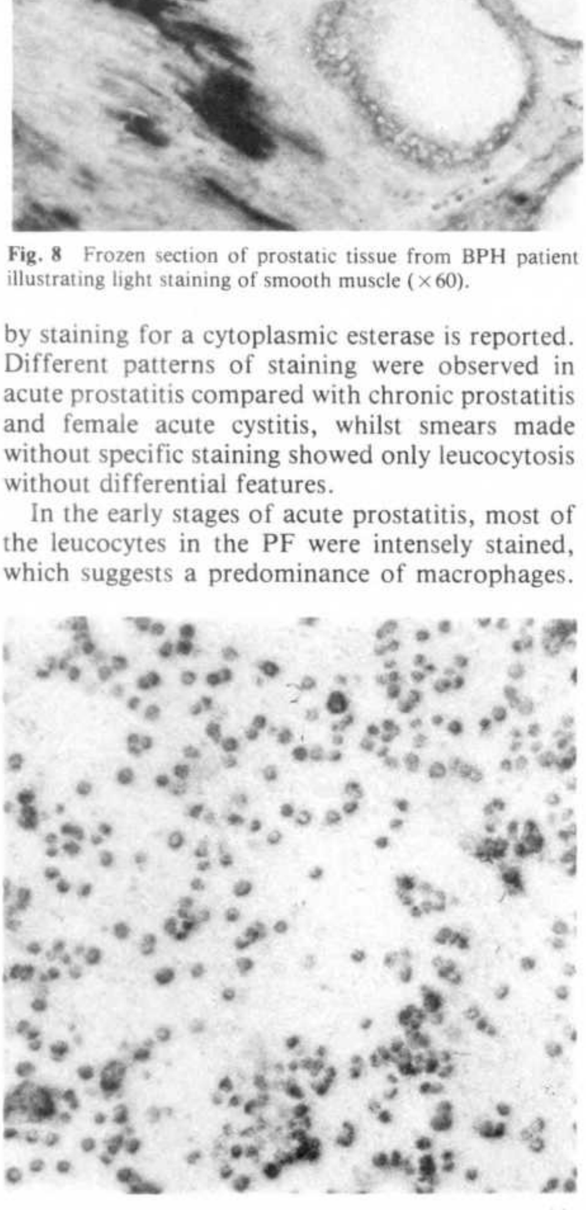

Fig. 9 Smear of urinary sediment from female acute cystitis patient (×100).

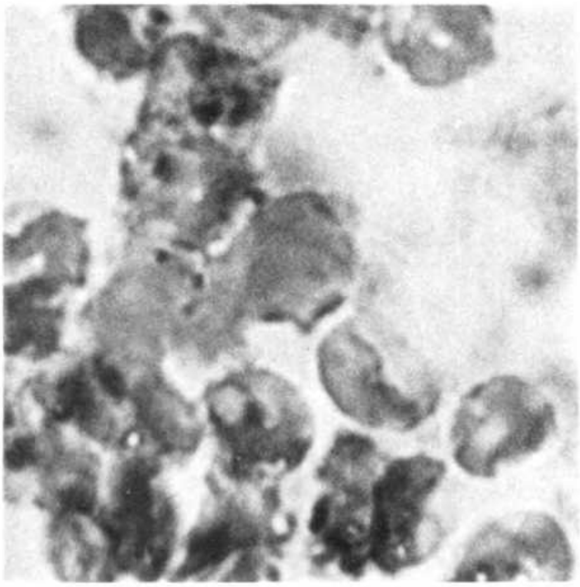

Fig. 10 Higher magnification (×1000) of section shown in Figure 9.

These findings correlate with the observations on dogs with acute prostatitis in which histological examination revealed the prostatic acini to be predominantly filled with macrophages (Baumueller and Madson, 1977).

In smears of PF from patients with chronic prostatitis, only a few leucocytes were stained. Frozen sections of prostatic tissue from patients with chronic prostatitis showed some macrophages around the acini, which appeared to be the source of the macrophages appearing in PF since they were similar in colour and shape. In addition to the macrophages, some of the stroma of the prostate took up the stain, especially smooth muscle, but this was much less intense, so that the macrophages could easily be distinguished. Staining of smooth muscle was also reported in a study of the distribution of non-specific esterase in mouse epididymis (Blecher and Kirkeby, 1978).

In female acute cystitis, none of the leucocytes in the urinary sediment was stained at any stage of the disease. The reason for this is not immediately clear and requires further study.

The differential staining of the leucocytes between each disease may be helpful in the initial diagnosis and follow-up of cases of prostatitis. Further study, including a longitudinal study, is in progress in an attempt to explain the mechanism and meaning of the appearance of these leucocytes in prostatitis.

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Urethral Strictures at Baragwanath Hospital

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Summary—The records of 258 patients operated on for urethral strictures at Baragwanath Hospital over a 40-month period were reviewed. The young, economically active man was mostly affected and gonorrhoea appeared to be the most frequent aetiological cause. Internal urethrotomy was the commonest procedure performed (64% of cases). Overall, a single procedure was done in 70% of the patients, whilst the remaining 30% had multiple operations. Eighty-eight per cent of the internal urethrotomies were successful. Good results were also seen with the other single-stage procedures, whilst a high percentage of 2-stage urethroplasties returned with complications. It is emphasised that the simplest, one-stage procedure necessitating the shortest hospital stay should be the elective treatment of choice in these patients.

John Hunter (1728-93) was the first person to record the incidence of site of urethral strictures, which he found to occur most frequently in the bulbous urethra. He noted that gonorrhoea was probably the most common cause of these strictures. The findings at Baragwanath Hospital have added remarkably little to Hunter's findings.

Baragwanath Hospital deals solely with black patients, mainly resident in the adjoining township of Soweto near Johannesburg, which has an estimated population of 1,250,000. Cystoscopic investigation and surgical treatment for urethral strictures comprise 14% of all urological procedures at this hospital.

Many of these patients are young males with dependent families. Taking into account their financial stringency and the need for treatment of their strictures, it is important that the simplest, most effective urological procedure with the shortest hospital stay should be a prime consideration.

The majority of these patients were admitted to hospital either with severe obstructive symptoms, retention of urine or extravasation and sepsis.

Patients

Two hundred and fifty-eight patients were treated surgically during the period 1.4.75 to 31.7.78. Strictures not requiring hospitalisation, or those treated with urethral dilatations, were not included in this series.

The fourth decade was the commonest age incidence at initial presentation, ranging from 9 to 98 years with a mean of 45.6 years (Fig.), and the commonest presenting features were urinary retention and perineal extravasation of urine with abscesses or progressive necrotising fasciitis (Table 1). These latter patients required emergency supportive measures, suprapubic urinary diversion and extensive debridement prior to definitive treatment of the strictures, with usually a prolonged hospital stay.

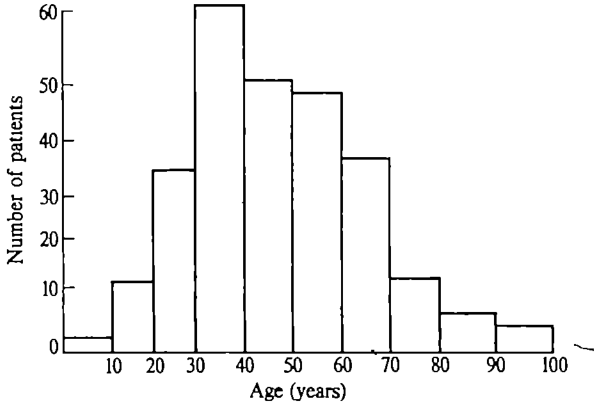

Fig. Age distribution.

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Table 1 Presenting Features

Urinary retention	48%
Perineal extravasation and complications	39%
Renal failure	9%
Bladder stones	2%

Table 2 Aetiological Factors

		102 Patients (40%)	
		Patients	*(%)*
Gonorrhoea		60	59
Trauma		27	26
Iatrogenic		10	10
Others			
Carcinoma of urethra	1 patient	5	5
Carcinoma of prostate	2 patients		
Condylomata acuminata	1 patient		
Congenital	1 patient		

In only 102 patients (40%) was the aetiology of the stricture established (Table 2). Histology, where obtained, was not helpful. Of special interest in the iatrogenic stricture group were 2 patients with strictures of the bulbous urethra following perineal urethrostomies for transurethral resection of the prostate.

The commonest sites of the stricture, where recorded (Table 3), were in the bulbous and bulbopenile urethra in 58 patients (65%) and the cause was presumed post-gonococcal in 39 patients (66%). A history of gonorrhoea was obtained in all 10 patients (16%) with multiple strictures.

Traumatic strictures were found in the membranous urethra in 15 patients (54%) and in the bulbous urethra in 11 patients (42%) and this correlated with the type of injury sustained. The only congenital stricture was situated in the penile urethra. This was a diaphragmatic stricture in an 11-year-old boy with enuresis as his main symptom.

Results

The commonest operation performed on 165 patients (64%) (Table 4) was an internal urethrotomy. The stricture was first negotiated with a filiform and then dilated sufficiently to enable an Otis urethrotome to be passed through the stricture. Incisions were made at 2 and 10 o'clock after opening the urethrotome to 35 FG. After the instrument was removed, a 22 FG Foley catheter was left in position for a period ranging from 5 to 7 days.

Of the open operations, 2-stage urethroplasties (15%), excision urethroplasty (8%) and free skin patch urethroplasty (5%) were the commonest operations. Six patients (2%) had a Badenoch pull-through procedure (Badenoch, 1950). One hundred and eighty-one patients (70%) had a single procedure, whilst the remaining 77 patients (30%) underwent multiple operations.

If taken into consideration that patients would return to Baragwanath Hospital only if the results were unsatisfactory, it can be surmised, perhaps optimistically, that those patients who did not return were either cured or satisfied with their results. Based on this assumption (Table 5) it would seem that the commonest single procedure, internal urethrotomy, gave satisfactory results in 145 patients (88%), whilst the remaining 12% returned for further treatment. Of the other one-stage procedures, 60% of the excision urethroplasty group (12 out of 20 patients) and 61% of the free skin patch urethroplasty group (8 out of 13 patients) appeared to be satisfied with their results. Four of the 6 patients having had the Badenoch urethroplasty required another procedure, which was usually an internal urethrotomy.

There was no correlation between the success of a single operative procedure and the aetiology of the stricture (Table 6). The commonest multiple procedure was the internal urethrotomy, which gave good results even when repeated. Internal

Table 3 Aetiology Related to Site of Stricture

	Penile	*Bulbous*	*Bulbopenile*	*Membranous*	*Multiple*
(60 pts) Gonorrhoea	10 (16%)	28 (47%)	11 (19%)	1 (2%)	10 (16%)
(27 pts) Trauma	0	11 (42%)	1 (4%)	15 (54%)	0
(10 pts) Iatrogenic	3 (30%)	6 (60%)	0	1 (10%)	0
(5 pts) Others	4 (80%)	1 (20%)	0	0	0
102 pts	17%	45%	11%	17%	10%

Table 4 Surgical Procedures

	No. of patients	*(%)*
Internal urethrotomy	165	64
Excision urethroplasty	20	8
Free skin patch urethroplasty	13	5
Badenoch urethroplasty	6	2
First-stage urethroplasty	14	5
Second-stage urethroplasty	25	10
Other procedures	14	5
	258	100

Table 5 Single Operative Procedures

181 patients (70%) had only 1 operation		
Internal urethrotomy	145/165 patients	88%
Excision urethroplasty	12/20 patients	60%
Free skin graft urethroplasty	8/13 patients	61%
Badenoch urethroplasty	2/6 patients	33%

urethrotomy was used in most of the failed single-stage open procedures, also with satisfactory results.

The default rate of patient follow-up was high and only 41% of patients returned to the clinic. Follow-up ranged from 3 to 36 months. Of those patients who did return to follow-up and could be objectively analysed, 27 patients who had one or more internal urethrotomies were well 4 to 24 months post-operatively and a further 3 required urethral dilatation as out-patients. Only 2 patients who had free skin graft urethroplasties were seen 12 to 36 months following this procedure and both were satisfied with the results and required no further treatment. Six patients who had excision urethroplasties were followed up for a period of 4 to 12 months and required no further treatment. Of 12 patients who had 2-stage urethroplasties and were followed up for 4 to 36 months, 4 (33%) had recurring problems such as stomal stenosis and recurrent strictures which required out-patient dilatation.

Discussion

Internal urethrotomies were popularised in the nineteenth century when Otis designed his urethrotome, a modified version of which we still use today. Katz and Waterhouse (1971) reported good results in 64% of 61 patients treated with internal urethrotomy. It is a simple procedure, requiring a short hospital stay with early rehabilitation. Where necessary, the procedure has been repeated with good results.

When internal urethrotomy fails, a short stricture amenable to a single-stage procedure is the treatment of choice. Devine *et al.* described the free skin patch urethroplasty in 1963. Lately, excellent results using this method have been reported by Betts *et al.* (1978). Excision urethroplasty, although not popular with certain authorities, has been used by Panagakis *et al.* (1978) in 42 patients.

It seems apparent that with the increasing incidence of gonococcal urethritis and trauma, both industrial and traffic, more urethral strictures can be expected. Therefore the simpler, one-stage procedure should be considered first before involving the patient in a multi-stage operation, expensive in time and money both to himself and the Health Service.

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Table 6 Relationship of Aetiology to Success of Single Procedure

	No. of patients					
	Gonorrhoea	*Trauma*	*Iatrogenic*	*Other*	*Unknown*	*Total*
Internal urethrotomy	35	15	6	2	87	145
Excision urethroplasty	3	2	0	0	7	12
Free skin graft urethroplasty	1	2	2	0	3	8
Badenoch urethroplasty	0	2	0	0	0	2
First-stage urethroplasty	7	0	0	2	5	14
						181

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The Doppler Stethoscope in the Diagnosis of Subclinical Varicocele

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Summary—Fifty-six patients (112 testicular cords) were examined using the Doppler stethoscope. Venous reflux was detected in all patients with a clinically obvious varicocele and in 77% of patients where a varicocele was suspected but not clinically demonstrated.

The incidence of bilateral varicoceles was 21%.

The Doppler stethoscope showed that 20% of patients continued to have venous reflux post-operatively.

It is concluded that the Doppler stethoscope is a useful instrument in the diagnosis of clinical varicoceles and in the assessment of post-operative results.

A varicocele is an abnormality of the venous plexus of the spermatic cord and may present at different stages. In the advanced stage the diagnosis is easy and the varicocele feels like a bag of worms under the palpating fingers or, as described by Ambroise Paré (1510-1590), "like a group of vessels full of melancholic blood".

In about 30% of cases, a varicocele can be difficult to diagnose, appearing only as a simple impulse at the moment of coughing or with the Valsalva manoeuvre. This clinical diagnosis is all the more difficult when the cord is short or the patient is obese. When a subclinical varicocele is suspected, supporting evidence may be sought. Phlebography of the spermatic vein will show reflux in only 23% of cases and thermography will reveal a temperature difference of more than 1°C in only 36%.

We have evaluated the Doppler stethoscope in the diagnosis of varicocele according to the method suggested by Greenberg *et al.* (1977).

Materials and Methods

Fifty-six patients (112 testicular cords) were examined using the Doppler stethoscope. The cords were classified into 3 groups:

(1) No clinical evidence of varicocele (V0).
(2) Possible varicocele (V1).
(3) Definite varicocele on clinical examination (V2).

The Doppler probe was held with one hand on to the front of the testicular cord while the testis was supported with the other hand in order to prevent any involuntary movement. The pulse of the spermatic cord was evidence that the probe of the Doppler stethoscope was in front of the vascular pedicle of the testis.

A jelly was applied between the probe and the skin in order to improve contact. We did not shave the skin of the scrotum of these patients. Venous reflux was studied before and during the Valsalva manoeuvre, with the patient standing in a warm room and in an atmosphere which generated confidence. The probe was connected to 2 different types of apparatus: (1) directional, which enabled a complete recording, and (2) non-directional, which was less precise but gave a recording that was sufficient for out-patient measurement.

Results

The results have been classified into 4 groups:

(1) No reflux, but spermatic artery beating.
(2) Equivocal results.
(3) Reflux either spontaneously as a continuous humming noise or provoked by the Valsalva manoeuvre.
(4) Absent spermatic artery beat—indicating that the probe was not in front of the vascular pedicle.

The Doppler examination confirmed the presence of a clinically obvious varicocele in all cases (Table). When a varicocele was suspected, it was

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Table

	No. of cords	*Doppler result*			
		Positive	*Equivocal*	*Negative*	*No artery*
No varicocele (V0)	54	3	7	41	3
Possible varicocele (V1)	36	28	3	4	1
Definite varicocele (V2)	22	22	—	—	—

confirmed by the presence of reflux in 28 out of 36 cases. When the cord was thin and supple and a varicocele was not suspected, reflux was found in 3 out of 54 cords.

Discussion

Venous reflux was confirmed in all cases of clinically patent varicocele. In those patients where a varicocele was suspected, 77% were confirmed by Doppler examination. This finding leads to the concept of a subclinical varicocele where reflux is found in a cord which is suspected of having a varicocele. This concept has already been proposed, based on studies using thermography, but the Doppler stethoscope appears to be more sensitive.

Bilateral varicoceles were demonstrated in 9 of the 56 cases (16%), a figure that is close to the 14% observed by Amelar *et al.* (1977).

The Doppler stethoscope appears to be a very sensitive instrument for detecting both unilateral and bilateral varicoceles. In our experience it is more accurate than thermography and does not have the inconvenience of phlebography.

We have also studied a series of 20 patients with varicoceles examined by the Doppler method before and after operation. Eleven doubtful (V1) clinical varicoceles with a positive Doppler examination were cured by operation and had a negative Doppler after the operation. Nine patients had definite varicoceles (V2) with a positive Doppler test and had the following post-operative findings.

Five were cured clinically and had a negative Doppler examination, 2 were clinical failures and continued to have a positive Doppler examination, and 2 had no evidence of varicocele but continued to have a positive Doppler test.

Thus in this pre-operative and post-operative study there was a clinical failure rate of 10%, but a 20% failure rate if the Doppler was taken as the basis for reference.

These studies have demonstrated certain limitations. In particular there was a lack of correlation between the Doppler stethoscope findings and other methods of diagnosis, *e.g.* thermography, phlebography and spermiogram. However, a certain number of conclusions may be drawn.

Reflux could be demonstrated in all of the patent varicoceles.

A subclinical varicocele was demonstrated in 28 out of 36 patients in whom there was some doubt about the presence of a varicocele.

The Doppler appears to be a more sensitive method than other tests available for detecting bilateral varicoceles.

The Doppler stethoscope represents a simple means of determining the post-operative result.

The limitations of the method are mainly that the degree of reflux from the varicocele may not be demonstrated in all cases; the technique also requires a certain amount of patience as well as practice in locating the vascular plexus.

It is concluded that, in the absence of alternative methods for detecting the subclinical varicocele, the Doppler stethoscope provides a useful method for studying the individual patient and groups of patients.

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The Non-surgical Treatment of Peyronie's Disease

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Summary—Forty-five patients with Peyronie's disease are described. No patient received treatment for one year from the time of presentation. Three had a complete resolution of their symptoms and signs during this period. The remaining patients received injections of triamcinolone hexacetonide (Lederle) into the plaques at 6-weekly intervals for 36 weeks. Thirty-three per cent had complete or marked improvement in their symptoms; those responding were younger patients with small, firm, discrete plaques in the distal penis. We recommend a non-operative approach in this group. Surgery or chemotherapy should be reserved for those older patients with harder, larger or confluent plaques.

This condition was first described by François de la Peyronie in 1743. Since then many series have been reported and a variety of methods used for treatment. The clinical features of Peyronie's disease are well established, but the aetiology and the natural history of the disease, if left alone, are still unknown. Treatment of the condition remains an enigma to urologists. Williams and Thomas (1970), who reported 21 cases, felt that "Peyronie's disease is fully manifest when the patient is first seen". No patient in their series became worse and the natural history was one of resolution, albeit over many months.

We report a series of 45 patients seen by one of us (N.A.G.) over a 10-year period from 1964 to 1974 with a minimum follow-up of 4 years. We have tried to determine those features of the condition which may lead to spontaneous improvement and those which may indicate that some form of treatment will be required.

Patients and Methods

There were 45 patients whose age at presentation ranged from 32 to 78 years with a mean of 57 years (Fig.). A detailed family history was taken from each patient to determine whether there was any association between Peyronie's disease and collagen disorders, gout and Dupuytren's diathesis. The latter may present as a spectrum of manifestations ranging from nodule formation in the palmar fascia alone to the complete syndrome of palmar contracture, fibrous plantar nodules and Garrod's pads—the knuckle pads over the dorsum of the interphalangeal joints (Garrod, 1904; Lettin, 1964).

The history where deformity of the penis occurred was directed towards the type of deviation of the penis during erection. Direct questioning as to whether sexual intercourse was possible or not was recorded in an attempt to evaluate whether this improved with or without treatment. Presenting symptoms, whether of pain, plaque or deformity, were noted. The site, size and consistency of the main plaque or plaques were also recorded. The plaques were classified as being either hard or firm in consistency, confluent or diffuse, multiple or discrete. Blood was taken for haemoglobin, white count, ESR, tests of liver and renal function, uric acid and rheumatoid factors. X-rays of the chest and penis were carried out on all patients.

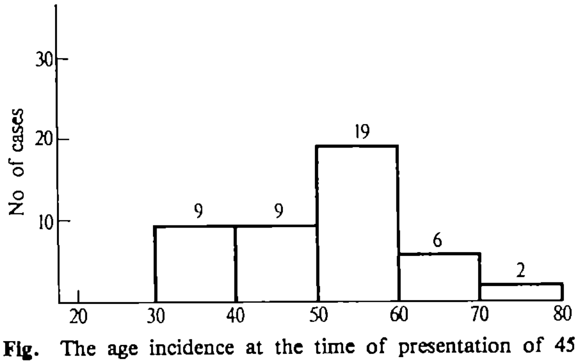

Fig. The age incidence at the time of presentation of 45 patients with Peyronie's disease.

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Table 1 Peyronie's Disease—Incidence of Other Diseases (Dupuytren's, Gout, Collagen Diseases)

Age	*Number*
30-40	5 out of 9
41-50	6 out of 9
51-60	9 out of 19
61-70	5 out of 6
70+	2 out of 2
Total	27 out of 45

Treatment

No patient received any form of therapy for one year from the time of presentation. Those patients who failed to undergo spontaneous improvement during this period were treated in the out-patient department by a direct injection of triamcinolone hexacetonide into or around the plaque using a small syringe with a fine needle, aiming to inject the steroid by slow injection into the plaque and the tissues immediately adjacent to it. A local anaesthetic agent was not used. A dose of 2 mg was injected into each plaque at 6-weekly intervals for a total of 6 injections. No patient in this series has been treated by surgery or chemotherapy.

Results

The Incidence of Collagen and Related Disorders

Twelve of the 45 patients gave a definite history suggestive of Dupuytren's diathesis, collagen disease or gout having occurred in their parents or siblings. Twenty-seven of the 45 patients (60%) with Peyronie's disease, in this series, were found to have one or more of these associated disorders when they first presented (Table 1).

Presenting Symptoms (Table 2)

Pain and deformity were the most frequent symptoms in this group of patients. In 16 patients the plaque was only noticed when pointed out to the patient. The plaques were situated near the glans in 12, in the shaft in 31, and at the base of the penis in 2 patients.

Table 2 Peyronie's Disease

Presenting symptoms	*No. of patients*
Pain, plaque, deformity	4
Pain, plaque	3
Pain	15
Plaque, deformity	1
Plaque	6
Deformity	15
None	1

Table 3 Peyronie's Disease. Nature of Plaque—Recovery or Improvement

Age	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*
Discrete	8/9	3/8	0/15	1/5	0/2
Multiple		0/1	1/4		
Confluent				1/1	

Course of the Disease

The patients were assessed as follows:

(*a*) Complete recovery of all presenting symptoms and signs.
(*b*) Marked recovery—a reduction in plaque size, pain or deviation, or complete resolution of 2 when all 3 were present.
(*c*) Slight improvement—some improvement in symptoms and signs.
(*d*) No improvement or progression of disease.

Spontaneous improvement occurred in only 3 of the 45 patients in the initial 12-month period when they received no treatment. These 3 patients were all below the age of 50, had a single small plaque near the glans which was firm in consistency, and no family history or personal evidence of a collagen disease. After treatment by injection with triamcinolone, a further 14 patients showed complete recovery or marked improvement in their condition. Those who responded were in the younger age groups with firm, discrete plaques measuring less than 2 cm (Table 3). Response to treatment took place during the course of the injections, *i.e.* within 36 weeks. It was unusual to notice any further improvement after the injections finished. Fifty per cent of those who responded did so within 18 weeks. Of the 12 patients who were found to have hard plaques, 4 showed slight improvement; the remainder showed either no response or progression of the disease. Pain, when present, improved first of all and most consistently, the plaque being the next symptom or sign to improve and deformity last of all. Thirty of the 45 patients found sexual intercourse to be possible when they first presented. The majority of these patients were in the under-60 age group. In those who responded to treatment by injection, sexual intercourse became more satisfactory, particularly in those with relief of pain. In general, haematological and biochemical investigations were of little value. Three patients had a raised serum uric acid and 3 positive rheumatoid factor. Radiography of the penis showed calcification to be present in a plaque in only one case.

Discussion

Since Peyronie's initial description of this disease, a considerable volume of literature has accumulated. The aetiology of the disease is still unknown. It has been suggested that it is an expression of premature ageing of connective tissue which has received repeated small vascular insults (Desanctis and Furey, 1967). There seems to be a connection with the fibrous involvement observed in Dupuytren's diathesis. Gallizia (1964) reported that 10% of patients with Peyronie's disease have a coexistent Dupuytren's contracture. In our series, the coexistence of Dupuytren's diathesis with Peyronie's disease was much higher at 47%.

The maximum incidence of the disease occurred between the fortieth and sixtieth year and is similar to that reported by Ashworth (1960) and Pugh (1960). There is no difference in this series in the clinical findings which were reviewed by McRoberts (1969). A higher proportion of plaques occurred in the distal penis in our patients. In other larger series, an equal incidence has been reported, plaques occurring throughout the length of the penis but not in the glans (Pugh, 1960).

An objective evaluation of a particular type of treatment is hampered by the lack of untreated controls. Ashworth (1960) published a series of 32 patients, 11 of whom were untreated and 8 of these were observed for periods of up to 5 years. On the basis of these 8 patients and the remaining treated patients, he believed that "the onset of Peyronie's disease heralds the end of effective sexual life". However, Williams and Thomas (1970), in their series of 21 patients, concluded that Peyronie's disease is fully manifest when the patients are first seen. Six of their patients' symptoms resolved completely without treatment, 10 improved so that sexual intercourse was possible and 5 remained unchanged. The average period for resolution in their series, however, was 4 years.

We have tried to determine those features of the condition which might indicate spontaneous improvement or an accelerated rate of improvement of symptoms.

It might be argued that a period of observation of one year is too short to assess the incidence of spontaneous improvement. However, we feel that a patient with pain and deformity of the penis should not be left for up to 4 years in the hope that spontaneous improvement may occur. Three patients, all below the age of 50, underwent spontaneous improvement within the first 12 months of observation, although all had small plaques (<2 cm) in the distal penis.

The use of steroid injections into the plaques has been extensively reported. Desanctis and Furey (1967) noted that 81% of their patients treated by steroid injections benefited to a moderate or marked degree. Triamcinolone hexacetonide is a long-acting glucocorticoid with low solubility, producing, in theory, maximal local action with minimal side effects. It has been shown to be effective in the treatment of Dupuytren's contracture and hypertrophic scars. Of the 42 patients who received injections of this drug, 33% had complete recovery or marked improvement in their symptoms and signs during the course of treatment. Twelve of these patients were below the age of 50 with firm, discrete plaques measuring less than 2 cm in the shaft or distal penis. Patients with hard or larger plaques and those with associated collagen disorders were unlikely to respond to this form of treatment. Whether those patients who responded to steroid injections would have improved spontaneously if left untreated for longer periods will remain unknown. However, there were no complications or side effects in this method of treatment and the speed of response was encouraging.

Chemotherapy or surgery should be considered only for older patients with hard, multiple or confluent plaques. Procarbazine, a cytostatic drug, has been used to treat 24 patients with Peyronie's disease (Chesney, 1975). Good results were reported in 11. The drug is also a monoamine oxidase inhibitor and should be administered with caution. Severe bone marrow depression may occur and there is experimental evidence that the drug can cause damage to the germinal epithelium of the testes. In his series, 3 patients still had complete azoospermia at the end of their treatment 3 months later. Potassium para-amino benzoate (Potaba) has also been used (Hasche-Klunder, 1970). This involves taking 12 g of the drug each day for at least 6 to 12 months for maximum response. The action of the drug is antagonised by sulphonamides, and anorexia and nausea may occur during the course of therapy. Treatment by local injection involved a shorter course of treatment and was free of side effects.

We feel that in younger patients with small, firm plaques, the conservative approach to management should be adopted.

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Flexible Fibre-endoscopy of the Ileal Loop

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Summary—Three cases are described in which conventional radiology had suggested that recurrent tumour was present at a ureteroileal anastomosis. Fibre-endoscopy of the ileal conduits was performed with the Olympus short colonoscope. In each case the anastomosis was seen to be normal and no complications ensued.

It is suggested that fibre-endoscopy of the urinary conduit is a safe and simple adjunct to conventional radiology.

Haematuria occurring after ileal conduit urinary diversion for malignant disease of the bladder must arouse the suspicion that tumour has recurred in the remaining urothelium or in the conduit. A recent review described 4 instances of tumour arising in association with ileal conduits and described a further case of papillary carcinoma which had developed at the site of the ureteroileal anastomosis (Banigo *et al.*, 1975). Tumour has also been reported in an ileal conduit performed for exstrophy of the bladder (Shousha *et al.*, 1978). Excretion urography, antegrade pyelography and ascending pyelography via the ileal loop provide satisfactory assessment of the upper tracts, but problems may be encountered in the interpretation of filling defects seen at the ureteroileal anastomosis. The value of urinary cytology in screening patients after urinary diversion has been emphasised (Soloway *et al.*, 1972), but interpretation may be difficult after irradiation or in the presence of infection.

The use of the flexible fibreoptic gastroscope has been reported previously (Ramsburgh *et al.*, 1976), but has received little attention in this country. Of the 7 cases originally described, 3 had undergone ureterosigmoidostomy, 3 had undergone ureteroileostomy and one had undergone cutaneous ileocystostomy. The indications for examination included bleeding, post-operative urinary leakage and late ureteric stenosis. In each case the results of conventional radiography had been equivocal. The sources of bleeding were located by endoscopy and in one case retrograde ureteric catheterisation was performed.

We report a further 3 cases in which fibre-endoscopy has been a safe and valuable adjunct to conventional methods of investigation.

Case Reports

Case 1. A 46-year-old female underwent radical cystectomy in 1973 for multifocal, T2 transitional cell carcinoma of the bladder. The ureters were transplanted into an ileal conduit by the Wallace technique (Wallace, 1966). An excretory urogram and ascending pyelogram via the loop had demonstrated a filling defect in the

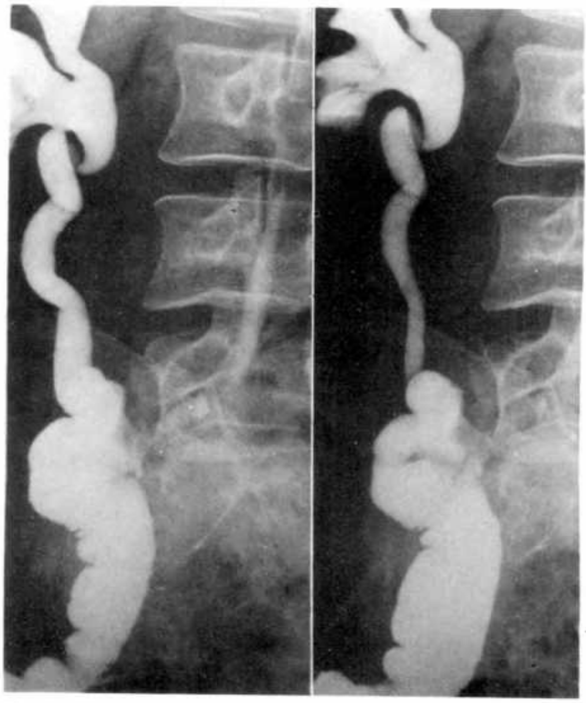

Fig. 1 Excretory urogram suggesting a filling defect at the lower end of the left ureter.

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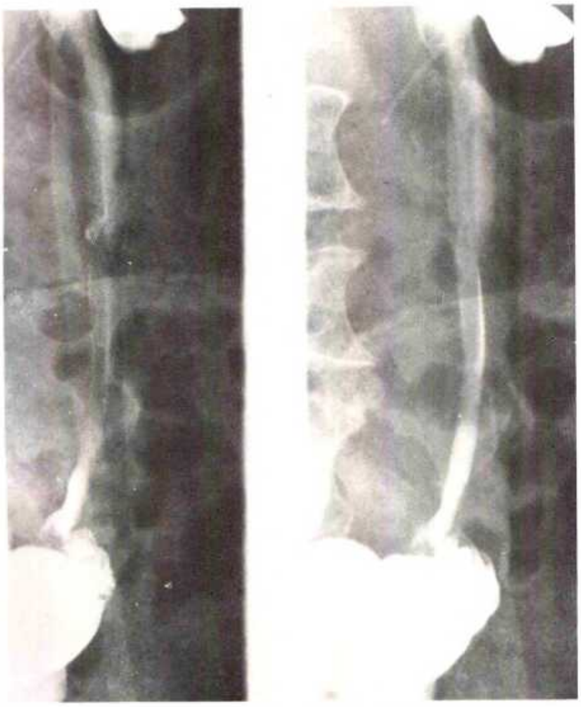

Fig. 2 Excretory urogram showing a silastic tube in the left ureter with a filling defect at the lower end.

right renal pelvis consistent with a stone. There was also a filling defect at the lower end of the left ureter which was thought to be a tumour (Fig. 1). Cytological examination of the urine was negative for malignant cells. Premedication with atropine 0.6 mg and diazepam 10 mg intramuscularly was given one hour before the examination, which was performed with an Olympus short colonoscope. Its introduction was facilitated by gentle dilatation of the stoma to size 40 Hegar. The instrument was then advanced under direct vision to 35 cm and troublesome peristalsis was abolished by the intravenous administration of Buscopan 20 mg. The entire length of the loop and ureteroileal anastomosis were well visualised and no tumour was seen. A pyelolithotomy was subsequently performed and there has been no further haematuria.

Case 2. A 77-year-old man underwent an ileal loop urinary diversion in 1977 for intractable irradiation cystitis and recurrent transitional cell carcinoma of the bladder. His post-operative progress was complicated by the loss into the loop of the silastic tubes used to splint the ureteroileal anastomosis. In view of his age, it was decided to leave the tubes *in situ*. He continued to bleed intermittently from the urethra, but this was controlled by repeated formalinisation of the bladder. However, in August 1978 he developed continuous urethral bleeding and haematuria from his ileal conduit. An excretory urogram showed the silastic tubes still present in both ureters but there was also a filling defect at the anastomosis (Fig. 2). The urinary cytology was reported to show cells suspicious of tumour recurrence. It was decided to treat the bladder with further palliative irradiation and to include the ureteroileal anastomosis in the field if tumour recurrence could be confirmed.

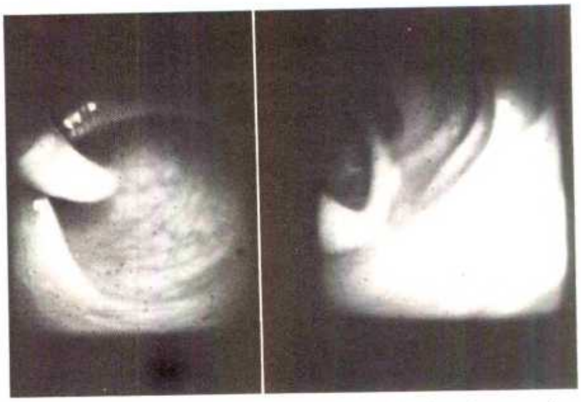

Fig. 3 Ureteroileal anastomosis with a silastic tube emerging from the ureteric orifice.

The loop was examined with the Olympus short colonoscope after premedication with atropine and diazepam. The instrument was passed easily to 40 cm after dilatation of the stoma and peristalsis was abolished by Buscopan. No tumour was seen at the anastomosis and the tubes were seen lying in the loop and emerging from the ureters (Fig. 3). The tubes were extracted as the instrument was withdrawn.

Case 3. A 72-year-old man underwent radical cystectomy and ileal loop diversion in February 1978 as a salvage procedure following radical radiotherapy. The left ureter was noted to be fibrotic and ischaemic at the time of operation. A routine excretory urogram repeated 6 months after his operation showed a left hydronephrosis and hydroureter. An antegrade pyelogram was performed and it suggested that there was a filling defect at the ureteroileal anastomosis, although the contrast flowed into the loop. Fibre-endoscopy of the loop showed a normal loop and no tumour was seen at the anastomosis.

Discussion

These cases illustrate the value of flexible fibre-endoscopy of the ileal loop as an adjunct to conventional radiology and urinary cytological examination. The patients tolerated the procedure well and no problems were encountered in examining the entire loop up to the anastomosis. The urine from each patient was checked for infection before the procedure and no problems were encountered with bacteriaemia or infection after the examination. In addition to its diagnostic value, the flexible fibreoptic instrument enables procedures such as biopsy, retrograde catheterisation and retrieval of foreign bodies to be performed.

Dilatation of the stoma facilitates the introduction of the instrument and provided that it is advanced under direct vision there should be little risk of perforating the loop. Peristalsis of the loop, which at times can be vigorous and may obscure the field, is abolished by the intravenous administration of an anticholinergic drug.

Flexible fibre-endoscopy of the ileal conduit appears to be a safe and simple procedure which may be usefully employed as an adjunct to conventional radiology. Provided that the simple technical points described are followed, there may be less risk of perforating the loop than by the introduction of a rigid panendoscope or cystoscope.

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Os Penis

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Os penis is such a rare condition that only 10 such histologically documented cases have been reported.

Case Report

A 55-year-old man had noticed an indurated area on the ventrum of the base of the penis of 3 years' duration. There was no history of previous illness, trauma to the penis or diabetes mellitus. He had noted diminished libido.

On examination there was an indurated firm plaque 1 cm wide on the mid-ventral aspect of the proximal third of the penis. Rectal examination was normal. An X-ray of the penis showed a piece of bone corresponding to the affected part (Figs. 1 and 2).

Comment

Eglitis (1953) in his review mentioned histologically proved cases of os penis. Subsequently 4 more were added by Gulati *et al.* (1974) but except for one case diagnosed in childhood (Champion and Wegarzyn, 1964) the rest were diagnosed in later life.

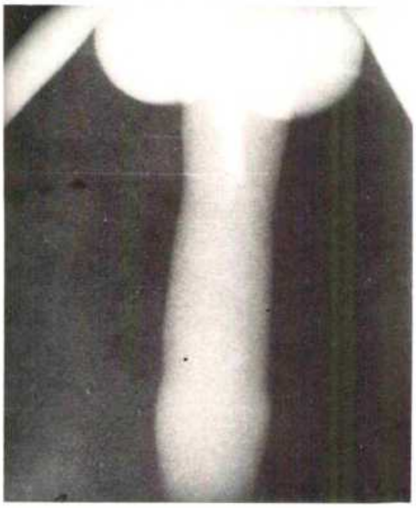

Fig. 1

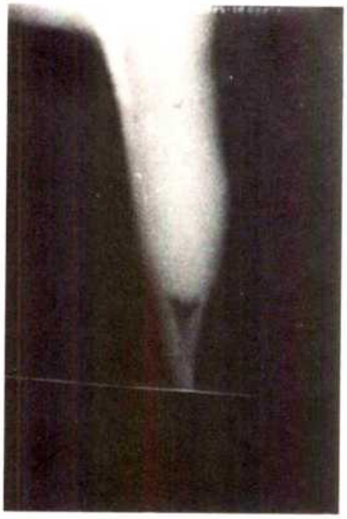

Fig. 2

Os penis appears to be a congenital condition which remains concealed until later life, when it attracts attention either because of chronic fibrous tissue reaction provoked over the bone or pain during erection.

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Ureterocele with Leiomyoma of Ureter

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Case Report

A 35-year-old lady was admitted with right flank pain of one year's duration. Excretory urogram showed the characteristic cobrahead appearances of a right-sided ureterocele (Fig. 1) with hydronephroureter. Exploration revealed a ureterocele 2 cm in length with a pinhole ureteric orifice on the affected side. The ureterocele was excised and ureteroneocystostomy was done, with post-operative symptomatic relief. Histopathology revealed a hypertrophic muscular coat and a leiomyomatous nodule at the lower end (Fig. 2).

Comment

Ureteroceles are considered to be due to congenital thinning and weakening of Waldeyers' fascia and the muscle coat, associated with partial obstruction to the lumen of the ureter which leads to cystic dilatation of the intramural portion of the ureter. The cause of obstruction to the flow of urine has not been conclusively proved.

The presence of a leiomyoma in the ureter causing partial urinary obstruction raises the possibility of a secondary ureterocele in this case. This is one of the rarest presentations of ureterocele because of the presence of a demonstrable cause of urinary obstruction. Morever, primary ureteric tumours themselves are rare (1% of all urinary tract tumours) and primary mesodermal tumours are the rarest (Scott and McDonald, 1970).

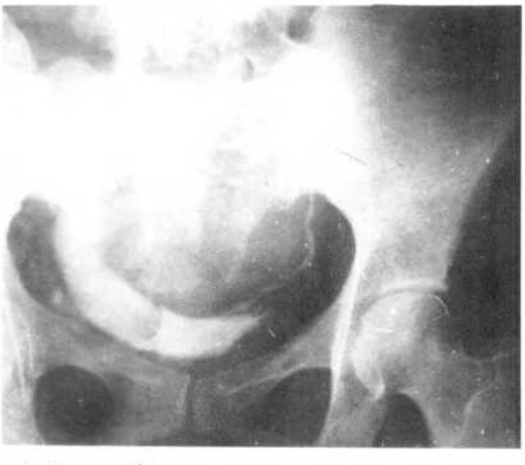

Fig. 1 Ureterocele.

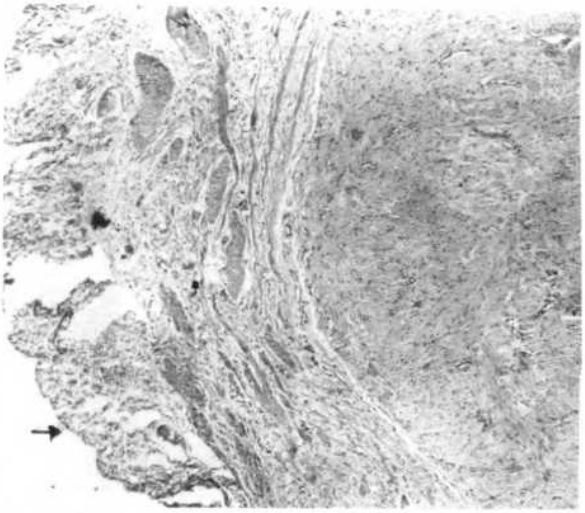

Fig. 2 Leiomyomatous nodule on hypertrophic wall of ureterocele (H and E ×44).

References

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Requests for reprints to: R. V. S. Yadav, Department of Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

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Primary Carcinoma *in situ* of Renal Pelvis and Ureter

M. STRAGIER, R. DESMET, H. DENYS, R. VERGISON and J. VANVUCHELEN, *Division of Urology and Cytopathology, St John's Hospital, Ruddershove, 8000 Brugge, Belgium*

A case of carcinoma *in situ* of the renal pelvis without previous or coincidental vesical neoplasm is presented. Such cases are extremely rare. We found only 5 reports in the literature. The essential role of cytopathology in diagnosis and follow-up is emphasised.

Case Report

A 63-year-old woman complained of intermittent painless haematuria for 3 weeks. Cystoscopy revealed no abnormality. Excretion urography showed a 4 cm cyst in a rotated right kidney. Neither cystography nor study of the fluid of the cyst suggested malignancy. Arteriography was normal. At retrograde pyelography a sample taken from the right renal pelvis after irrigation with saline contained malignant tumour cells corresponding with a papillary transitional cell carcinoma grade II-III, although no lesion was seen in the retrograde pyelogram. A right nephroureterectomy was performed.

Pathology

Gross The kidney weighed 148 g and contained a cyst; otherwise the parenchyma was unremarkable. The mucosa of the pelvis and calices was haemorrhagic.

Microscopic The mucosa of the pelvis contained multiple foci of flat carcinoma *in situ* with broad areas of denudation. The carcinomatous epithelial layers were composed of large hyperchromatic cells with an abnormally high rate of mitosis (Fig.) but did not invade the submucosa, which was oedematous and congested.

Cystoscopy 3 months after operation showed no lesions. Cytology after irrigation of the bladder was normal and we shall perform this examination at regular intervals.

Comment

Carcinoma *in situ* is well recognised in the bladder but rare in the pelvis alone. We are convinced that a number of such cases are not identified because cytological examination is either done on voided urine, which gives many false negative results (Cullen *et al.*, 1972; Wagle *et al.*, 1974) or not done at all. The sample must be taken after irrigation of the bladder or pelvis or by using a brush catheter at retrograde pyelography (Bibbo *et al.*, 1974).

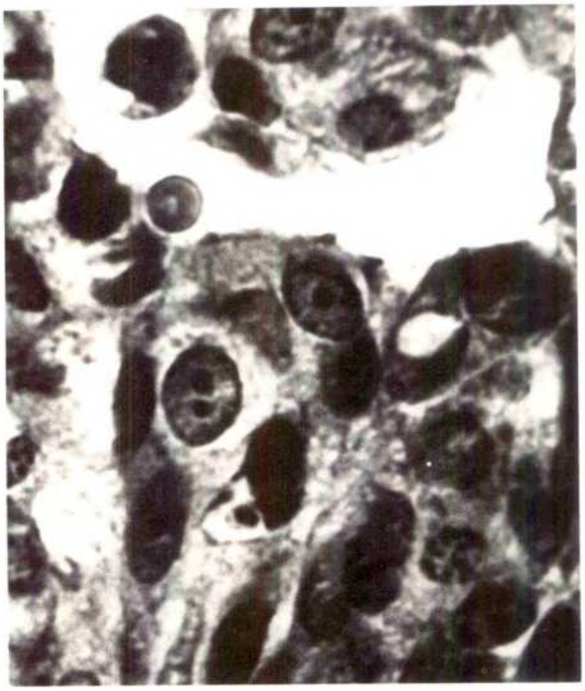

Fig. Flat carcinomatous epithelium: cellular pleomorphism and nuclear hyperchromicity. Note the shedded cells at the top (H and E ×400).

In patients with unexplained haematuria or dysuria, cytological examination after irrigation of the bladder should be performed. If negative, samples must also be taken from the renal pelvis by retrograde catheterisation. Post-operative, regular cytological examinations are mandatory.

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Bibbo, M., Gill, W. B. and Harris, M. J. (1974). Retrograde brushing as a diagnostic procedure of ureteral, renal pelvic and renal calyceal lesions. *Acta Cytologica,* **18**, 137-141.

Cullen, T. H., Popham, R. R. and Voss, H. J. (1972). Urine cytology and primary carcinoma of the renal pelvis and ureter. *Australian and New Zealand Journal of Surgery,* **41**, 230-236.

Wagle, D. G., Moore, R. H. and Murphy, G. P. (1974). Primary carcinoma of the renal pelvis. *Cancer,* **33**, 1642-1648.

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0007-1331/80/02950402$01.00

Palliative Effect of Cyproterone Acetate in Carcinoma of the Prostate with Widespread Metastatic Bone Disease

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Pain due to widespread carcinoma of the prostate is a distressing problem when the disease becomes refractory to conventional endocrine therapy. We report such a case in which a gratifying palliative response was obtained by the administration of cyproterone acetate (Androcur: Schering Chemicals Ltd).

Case History

A 58-year-old patient underwent transurethral resection of the prostate for symptoms of bladder neck obstruction in 1969. Histological examination showed a well-differentiated adenocarcinoma of the prostate. He was given stilboestrol (50 mg twice daily) from the day after operation and his condition remained satisfactory until 4 years later. At this time he developed venous thrombosis in the left calf and painful skeletal metastases. Oestrogen therapy was discontinued and bilateral orchiectomy performed. The bone pain was relieved, but returned 2 years later when the sclerotic metastases had become more widespread. The pain was severe, requiring frequent doses of analgesics and opiates, he became bed-ridden and lost weight rapidly. Radiotherapy to the spine did not relieve the pain. At this time his haemoglobin was 7 g/dl and the serum acid phosphatase 104 u/l. Oral cyproterone acetate (100 mg 3 times daily) was started and within 4 days all pain had gone. His sense of well-being returned, he was able to walk without discomfort and resume a normal life. After 6 months' therapy the haemoglobin had risen to 10.9 g/dl and the acid phosphatase had fallen to 55 u/l, but there was no obvious change in the radiographic appearance of the spinal metastases. The patient remained well, ambulant and pain-free for 10 months, when he developed an adenocarcinoma of the rectum for which anterior resection was performed. In the convalescent period the back pain returned and the acid phosphatase rose to 243 u/l. Treatment with cyproterone acetate was continued but his condition deteriorated and despite a course of cyclophosphamide he died 18 months after starting cyproterone acetate. Postmortem examination confirmed the presence of widespread skeletal deposits of carcinoma of the prostate.

Comment

Cyproterone acetate is an oral progestational steroid with a potent anti-androgen effect (Scott and Schirmer, 1966) which has been reported to produce regression of prostatic carcinoma without problems of painful gynaecomastia (Scott and Schirmer, 1966; Geller *et al.*, 1968). Subjective improvement, relief of bone pain due to metastases (Geller *et al.*, 1968; Smith *et al.*, 1973) and regression of soft tissue metastases have been described (Jameson, 1976).

We report this case because of the dramatic return to normal life of a patient who appeared moribund and in severe pain after other endocrine treatment had failed. Although some fall of the serum acid phosphatase levels did occur, there was no obvious improvement in the radiological appearance of the bone metastases.

The case history supports previous observations that cyproterone acetate can have beneficial effects when widespread carcinoma of the prostate has ceased to respond to conventional therapy. A further indication is in patients with prostatic carcinoma who are prone to or develop thromboembolic phenomena as a result of oestrogen therapy. The agent appears to have no harmful side effects.

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* Present address: Plymouth General Hospital.

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Author's Follow-up

Methotrexate Treatment for Advanced Bladder Cancer. A Review after 6 Years

R. R. HALL, *Department of Urology, Freeman Hospital, Newcastle upon Tyne NE7 7DN* and A. G. TURNER, *Department of Urology, Peterborough and Stamford Hospitals*

The most important development in the use of cytotoxic chemotherapy has been the use of these drugs as part of the initial treatment of cancer, rather than last resort therapy for metastatic disease (Hall *et al.*, 1974). During the past 6 years Methotrexate has been applied to bladder cancer in 3 different ways.

In an attempt to establish the efficacy of adjuvant chemotherapy for advanced disease Methotrexate has been combined with pre-operative radiation and cystectomy as primary treatment for T3 bladder carcinoma in a prospective randomised study based on the Royal Marsden Hospital, London. No results are available yet.

In the hope of obviating the mutilation of cystectomy and urinary diversion and the misery of local recurrence following radiotherapy or partial cystectomy, Socquet (1980) has combined high dose intravenous Methotrexate with partial cystectomy as initial treatment for T3a disease. Using 2000 mg Methotrexate IV with appropriate Leucovorin rescue repeated every 3 weeks for 6 months following partial cystectomy in 17 patients, the 2-year survival rate is 100%, all patients remaining tumour-free.

Methotrexate has been used for multiple, frequently recurring, T1 bladder tumours by administering 50 mg orally every week without Leucovorin for 18 months following initial endoscopic clearance of the bladder. In a pilot study of 17 patients, the incidence and frequency of tumour recurrence have been reduced considerably in the majority of patients, although average follow-up is only 10 months and the study is not yet complete (Hall *et al.*, 1980).

The proportion of patients with metastases who show evidence of tumour regression has been maintained with further experience (Turner, 1980). The number of patients in reported trials remains small, so that a further Phase II study of intramuscular Methotrexate is now being prepared by the European Organisation for Research in the Treatment of Cancer (EORTC). The optimum dose and frequency of administration of Methotrexate remain unknown. From our cumulative experience it is clear that it is a safe drug which is free of side effects if given carefully. A 50 mg oral dose may be taken every week at home and 100 mg intramuscularly may be given every 2 weeks by the District Nurse without undue risk. Intravenous regimes ranging from 300 mg/m^2 every 7 days to 2 g every 3 weeks, each with appropriate Leucovorin rescue, have proved equally safe and free of toxicity. With both medium and high dose schedules several partial remissions of many months' duration have been achieved with a very good quality of life. On the other hand, no patient has been cured of metastatic bladder cancer by this agent. No study has yet demonstrated an unequivocal role for Methotrexate in the management of bladder cancer. However, the investigative studies mentioned here show that it is being used in a much more rational way.

Both authors continue to employ Methotrexate because it is simple and safe to use and still appears to be as effective as any other cytotoxic agent. The precise use of Methotrexate in clinical urology has yet to be determined.

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Hall, R. R., Bloom, H. J. G., Freeman, J. E., Nawrocki, A. and Wallace, D. M. (1974). Methotrexate treatment for advanced bladder cancer. *British Journal of Urology*, **46**, 431-438.

Hall, R. R., Herring, D. W., McGill, A. C. and Gibb, I. (1980). Oral Methotrexate therapy for multiple superficial tumours of the bladder. *Cancer Treatment Reports*, **64**. (In press.)

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Turner, A. G. (1980). Methotrexate in advanced bladder cancer. *Cancer Treatment Reports*, **64**. (In press.)

British Journal of Urology (1980), 52, 404-405

Notices

British Association of Urological Surgeons

President: W. K. Yeates, MD, MS, FRCS

Annual Meeting: London, 8-10 July 1981.

Abstracts of papers to be considered by Council for this meeting should be submitted to the Honorary Secretary by 2 January 1981. An abstract must be typed on a single sheet of A4 paper and consist of no more than 200 words. U.K. contributors must submit 25 copies of their abstract: other contributors may send one copy only.

All correspondence to: J. L. Williams, FRCS, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Swiss Society of Urology: 36th Annual Meeting

Montreux, Switzerland. 16-18 October 1980.

Further particulars from: Prof. K. Bandhauer, Secrétaire de la SSU, Clinique urologique, Hôpital cantonal, CH-9007 St-Gallen.

Symposium on Bladder Cancer and Prostatitis

Glasgow. 31 October 1980.

Further information from: Mr E. S. Glen, Department of Urology, Southern General Hospital, Glasgow G51 4TF.

Institute of Urology (The University of London) Preliminary Announcement of Seminars to be held Autumn 1980 to Summer 1981

October 1980

Treatment of the unstable bladder. 1-day seminar.
The renal papilla. 1-day seminar.
Diagnosis and treatment of erectile impotence. 1-day seminar.

November 1980

Advances in renal transplantation. 1-day seminar.
Radioisotopes in urology and nephrology. 1-day seminar.
Upper tract endoscopy. 1-day seminar.

December 1980

Renal homeostasis. 1-day seminar.
Uroradiology weekend. 2-day seminar.

January to March 1981

The scientific basis of urological practice. 10-week course.

April or May 1981

Endoscopic surgery. 3-day seminar.

May or June 1981

Operative urology. 5-day course.

July 1981

Testicular tumours and tumour markers. 2-day seminar.

Practice of the Hospitals Attachments

Can be arranged in the periods September to December and April to July, and enable attendance as an observer at clinics and operating sessions, use of Institute museum, reading room and library, and participation in teaching programme. Fee £60 a month.

Applications to the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE (tel. 01-836 5361), from whom detailed programmes may be obtained.

Nordic Association for Andrology. Early Diagnosis of Testicular Cancer

Copenhagen, Denmark. 5-7 November 1980

A workshop and symposium dealing with testicular carcinoma *in situ*, epidemiology, clinical aspects of testicular tumours and the early diagnosis of testicular cancer. Papers will be presented by an international panel of experts.

Further particulars from: Dr N. E. Skakkebaek, Laboratory of Reproductive Biology, 4052 Rigshospitalet, Blegdamsvej 9, DK2100, Copenhagen Ø, Denmark.

Institute of Urology (The University of London) Ten Week Course on The Scientific Basis of Urological Practice

12 January-20 March 1981

A full-time non-residential course covering all aspects of urological practice undertaken at the Institute and its associated St Peter's Hospitals.

There will be discussion of the techniques used and the research being undertaken. Operations will be demonstrated by means of closed circuit TV.

The course is designed for specialists in the field and those undergoing training in urology. It has been approved under the Advanced Postgraduate Training Scheme.

Closing date for applications: 1 December 1980.

Fee: EEC and UK based applicants £500, applicants from all other countries £1200, subject to review.

For further details and application form contact: The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01-836 5361.

Danish Urological Society. Second Copenhagen Symposium on Transurethral Surgery

Copenhagen, Denmark. 26-30 January 1981.

Further particulars from: Dr Finn Rasmussen, Department of Urology, Herlev Hospital, DK-2730 Herlev, Denmark. Closing date 1 December 1980.

First Meeting. Urological Days of Necker.

Paris, France. 12-14 March 1981.

The topics are:

(1) Tumours of calices, renal pelvis and ureter.
(2) Ureteropelvic junction obstructive anomalies.

The mornings of 12 and 13 March will be devoted to televised operations. The afternoons of these 2 days and the morning of 14 March will be devoted to communications. Each speaker will have 30 minutes at his disposal and the lectures will be published as monographs by Masson.

Further information from: Secrétariat des Journées Urologiques de Necker, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

American Fertility Society Meeting

Atlanta, USA. 14-18 March 1981.

The American Cystoscope Makers, Inc. (ACMI) will again sponsor an essay contest for the above meeting. Urology Residents, Fellows, and Urologists who have completed training within the past 5 years are eligible. The prize will be an $800 gift certificate for ACMI equipment. The work must be that of the author and not previously reported. Work on male reproduction or sterilisation should be submitted by 1 December 1980 to Dr Rodney A. Appell, Department of Urology, LSU Medical Center, 1542 Tulane Avenue, New Orleans, LA 70112, USA.

The Urological Society of Australasia. Annual Scientific Meeting

Sydney, Australia. 22-27 March 1981.

Further particulars from: P. O. Maher, Hon. Secretary, 10 Wybalena Road, Hunters Hill 2110, New South Wales, Australia.

Second Congress of the International Society of Urologic Endoscopy

Bristol. 9-11 September 1981.

Those wishing to join the Society should contact the Honorary Secretary, Dr Jorge Morera, Federico Lacroze 2154, (1426) Buenos Aires, Argentina.

Those interested in attending the meeting should contact Miss Sarah Storie-Pugh, Conference Services Ltd, 3 Bute Street, London SW7 3EY.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

British Journal of Urology (1980), **52**, 406

Mr R. A. Mogg, VRD, KSS, MCh, FRCS

Richard Arthur ("Dick") Mogg, President of the British Association of Urological Surgeons from 1974 to 1976, died on 13 June at the age of 68. He established the speciality of urology in the Principality of Wales as early as 1946, when he was appointed Consultant Urologist to the United Cardiff Hospitals. He gave loyal and unstinted service to our Council for 13 years in all, including the Honorary Treasurership and as a member of the Executive Committee of the journal he gave wise as well as witty counsel attending with conscientious regularity for 18 years. He was President of the Section of Urology of the Royal Society of Medicine (1970) and was an enthusiastic Secretary and chief organiser of the Urological Club of Great Britain for 12 years.

On the outbreak of the 1939 war, he spent 3 years at sea, during which time he was surgeon to a hospital ship and was landed at Crete in a mobile field hospital to treat and subsequently evacuate the casualties resulting from the German invasion. In 1942 at Haslar, he worked with Mr J. G. Sandrey, who was Consultant Urologist to the Royal Navy. It was at this time he wrote on the subject of gunshot wounds of the bladder. At the end of the war he was posted to Australia as Urological Specialist, where he established a life-long association with the urologists of Australasia. He was decorated VRD.

His clinical and academic interests centred largely on urinary diversion by colonic conduits, urinary tract injuries and paediatric urology, with particular reference to congenital anomalies and tumours of the urinary tract in children. His enormous urological practice produced a wide variety of clinical experience as well as a source of remarkably bizarre conditions, which he enjoyed reporting at clinical meetings with a sporting air of one-upmanship. He travelled widely and was invited to America on 5 occasions as Visiting Professor to 4 different university urological centres. He was Hunterian Professor, Abraham Colles Lecturer, RCS Ireland, and Hugh Young Orator of the American Urological Association.

Perhaps the honour that gave him the greatest pleasure was his appointment as Knight of the Order of St Sylvester, a papal Knighthood given on unique occasions to a distinguished non-Catholic.

Despite his extremely busy practice, Dick could always find time to listen with sympathy and understanding. He was loved by his patients and respected by his colleagues for his clinical and surgical ability combined with a positive affection for the man himself. His wit and good humour endeared him to both those he strove to cure and those with whom he worked. Dick had many other interests, enjoying carpentry and gardening and his Presidency of the Cardiff Food and Wine Society indicates the standard of his knowledge of cuisine and cellar. Music and, in particular, orchestral concerts were a great pleasure to him.

His loyalty to the speciality of urology was surpassed only by his affection and devotion to his family. He and his wife, Rosemary, were very close and happy and travelled together to most meetings. She supported him in all his professional and social life and her tragic death one year after his retirement left him very lonely in his last 2 years. Their 3 sons, of whom they were both justly proud, were a great comfort to him.

Urologists in this country and in the world have lost a distinguished colleague and friend and Wales has lost one of her greatest medical ambassadors.

J.P.M.

British Journal of Urology (1980), **52**, 407-408

Book Reviews

Uroradiology. T. Sherwood, A. J. Davidson and L. B. Talner. Pp. vii + 351. Oxford: Blackwell Scientific Publications, 1980. Price £35.00.

The book comprises 4 parts. The first describes the techniques of radiology and ultrasound; the second has a chapter on nuclear medicine by L. B. Talner and one on computed tomography by A. J. Davidson; the third is devoted to hypertension and consists of 12 pages written by L. B. Talner; the fourth part (all written, like the first part, by Thomas Sherwood himself) runs to 260 pages and describes the uroradiology of the diseased kidney, ureter, bladder, urethra and male genital tract.

"I wanted", writes the author, "to give FRCR candidates and others a personal view of what is interesting and important about uroradiology." He has certainly achieved that and very much more. It is a superb book and should be available to all involved in the management of patients with urological disease, be they radiologists, surgeons, urologists or physicians.

Tutorials in Postgraduate Medicine: Urology. Edited by G. D. Chisholm. Pp. 517 + xiii. London: Heinemann, 1980. Price £17.95.

This is an excellent multi-author book with contributions from all parts of the United Kingdom and also from the United States of America. Three topics have been selected for discussion—infection, stone and malignancy. Each topic is discussed by 5 or 6 authorities who each deal with a particular aspect of the subject. Then there is a section on the diagnostic approach to certain symptomatic features such as obstruction, incontinence and infertility, and finally a section in which various operative procedures are compared.

Each chapter presents the perfect examination answer to any question on that particular subject. For example, the candidate asked fo discuss biopsy may find himself at a loss after giving a brief review of the comparative values of aspiration needle biopsy and drill biopsy, but the chapter on this subject deals with it systematically and logically, giving the candidate a well constructed plan on which to base his answer.

There are a few minor criticisms. In the discussion on slow decompression of the atonic bladder, for instance, no mention is made of the extreme difficulty in monitoring such a decompression so that the nursing staff can ensure that pressure in the distended bladder is reduced gradually. On the subject of injuries to the kidneys the retrograde pyelogram is said to have been replaced by the improved excretory urogram, but surely the reason for condemning the retrograde was its risk of introducing infection into the area of the renal haematoma?

Each chapter constitutes one tutorial or lecture and in every chapter even the most experienced urologist will find something of interest and perhaps something new. It was surprising to read that the ureters are damaged in no less than 10% of all Wertheim's hysterectomies. This book is not intended as a comprehensive study of urology, but it does cover most of the controversial items with which either an examination candidate or a post-fellowship trainee may be faced.

The book is well produced, with a comfortable size of page and print. Illustrations are limited in number but are meaningful and well designed. It will be found extremely useful by any house surgeon on a urological ward, by a candidate preparing for the FRCS examination or by a post-fellowship trainee in urology, and it would still be of interest to most consultants in urology.

Campbell's Urology. Edited by J. H. Harrison, R. F. Gittes, A. D. Perlmutter, T. A. Stamey and P. C. Walsh. Fourth edition. Volume 2: pp. xxii + 1950. Volume 3: pp. xix + 1953-2640. Philadelphia: Saunders, 1979. Price £35.00 per volume.

The second volume has sections on benign prostatic hypertrophy, tumours of the genitourinary tract (what a pity that more is not written about the TNM classification even if the authors do not approve of it), embryology, congenital anomalies (including genetic determinants), neurogenic bladder, paediatric urology and behavioural aspects of urology. Forty-three authors contributed to this volume and this has led to a problem of uniformity. Although all are experts in the field about which they write, their abilities to communicate vary and there is some overlap, particularly between the sections on congenital anomalies and paediatric urology. However, it is better that things are said twice than not at all.

Volume 3 covers urological disease of the kidney, including renal transplantation and extracorporeal surgery, diseases of the ureter, urinary diversion, the surgery of incontinence, prostatectomy (including transurethral surgery), surgery of the penis, urethra and seminal vesicles, testicular neoplasms, the management of urinary problems during pregnancy, the role of radiotherapy and surgery of the adrenals. Each section is written by an acknowledged expert, mostly from the United States of America. The book is particularly valuable to a British department because both urological practice and surgical technique are fully covered; thus transatlantic differences in practice, *e.g.* retroperitoneal lymphadenectomy for non-seminomatous germ cell testicular tumours, can be more readily understood and the exact operative technique visualised. Each section is well referenced.

The production of this book is of the highest quality and, like the 3 previous editions, it remains one of the best reference books in urology.

Progress in Radio-oncology. International Symposium, Baden, 1978. Edited by K.-H. Kärcher, H. D. Kogelnik and H. J. Meyer. Pp. viii + 168. Stuttgart: Georg Thieme Verlag, 1980. Price DM 68.00.

This publication reports an international symposium held in 1978 which was directed at the methods now available for improving radiation therapy. The reader should not expect it to be the last word on this subject but he will find an interesting, up-to-date discussion on 5 main topics: neutron irradiation, immunology, sensitisers, hyperthermia and oxygen. Urologists interested in radiotherapy in uro-oncology will find that this report is reassuring evidence of the continuing efforts to improve this form of treatment.

Renal and Adrenal Tumours. Pathology, Radiology, Ultrasonography, Therapy, Immunology. Edited by E. Löhr. Pp. xviii + 372. Berlin: Springer-Verlag, 1979. Price DM 198.00; approx. US$ 110.90.

Thirty-four authors contributed to this book, which describes contemporary views on the pathology, diagnosis and treatment of renal and adrenal tumours. Transitional cell tumours, however, are mentioned only briefly in the chapters on pathology and ultrasound, and angiography. Most of the book is devoted to diagnosis and discusses, with many beautifully reproduced illustrations, the value of radiology, ultrasound, CAT scanning and nuclear medicine. Apart from 3 separate chapters on embolisation of the renal artery before or instead of surgery, not a lot of space is devoted to treatment. The book concludes with 33 pages of references (up to 1975), including many British and American, and is almost worth having for that alone—but it is expensive.

Models for Prostate Cancer. Progress in Clinical and Biological Research. Volume 37. Edited by G. P. Murphy. Pp. xii + 394. New York: A. R. Liss, 1980. Price US$40.00. (Available in United Kingdom, Europe and Middle East through European Book Service, Flevolaan 36-38, P.O.B. 124, 1380 Weesp, Holland. Price Dfl 120.00.)

This book records a meeting organised by the National Prostatic Cancer Project in Buffalo, New York, in May 1979. Thus, with commendable speed, this detailed text of nearly 400 pages is available for all those interested in experimental models for prostate research.

There are 2 main sections—one describes *in vitro* model systems using cell lines and organ culture and the other describes the animal models of adenocarcinoma in the rat. Although much of the contents describe the development and characterisation of these models, there is now sufficient experience with these models to see just where they stand for future use in research. Thus there is an encouraging amount of discussion on their potential clinical relevance. This is a highly recommended book on this subject.

Books Received

Hormonal Function and the Kidney. (Contemporary Issues in Nephrology, Volume 4.) Edited by B. M. Brenner and J. H. Stein. Pp. viii + 296. Edinburgh: Churchill Livingstone, 1979. Price £17.00.

Renal Dysfunction: Mechanisms Involved in Fluid and Solute Imbalance. H. Valtin. Pp. xvi + 499. Boston: Little, Brown and Co., 1979. Price $12.50.

Microsurgery. S. J. Silber. Pp. xxii + 492. Baltimore: Williams and Wilkins, 1979. Price £41.20; $61.50.

Genitourinary Radiology Case Studies. T. H. Johnson. Pp. 334. New York: Medical Examination Publishing Co., 1979. Price US$15.00.

Kidney Disease Case Studies. A. E. Parrish. Second edition. Pp. 280. New York: Medical Examination Publishing Co., 1980. Price US$13.75.

La Chirurgie du Rein Unique. J. Aubert. Pp. 252. Paris: Masson, 1979.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which the papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal.

A general section is included at the end.

ADRENAL

New simplified approach to diagnosis of pheochromocytoma. (B. H. Stewart *et al.*) *J. Urol.* 1979, **122**, 579.

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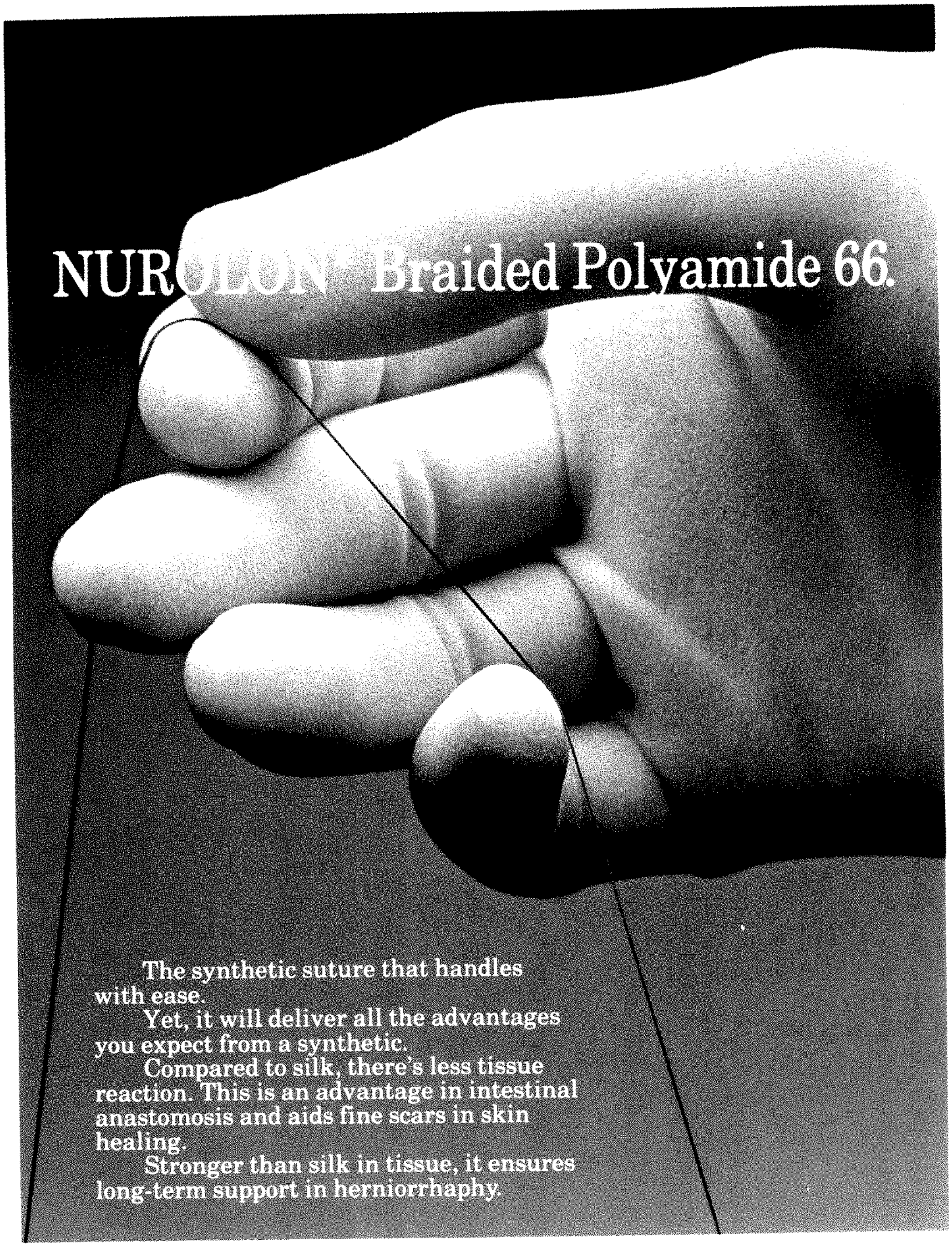

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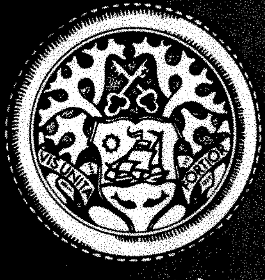

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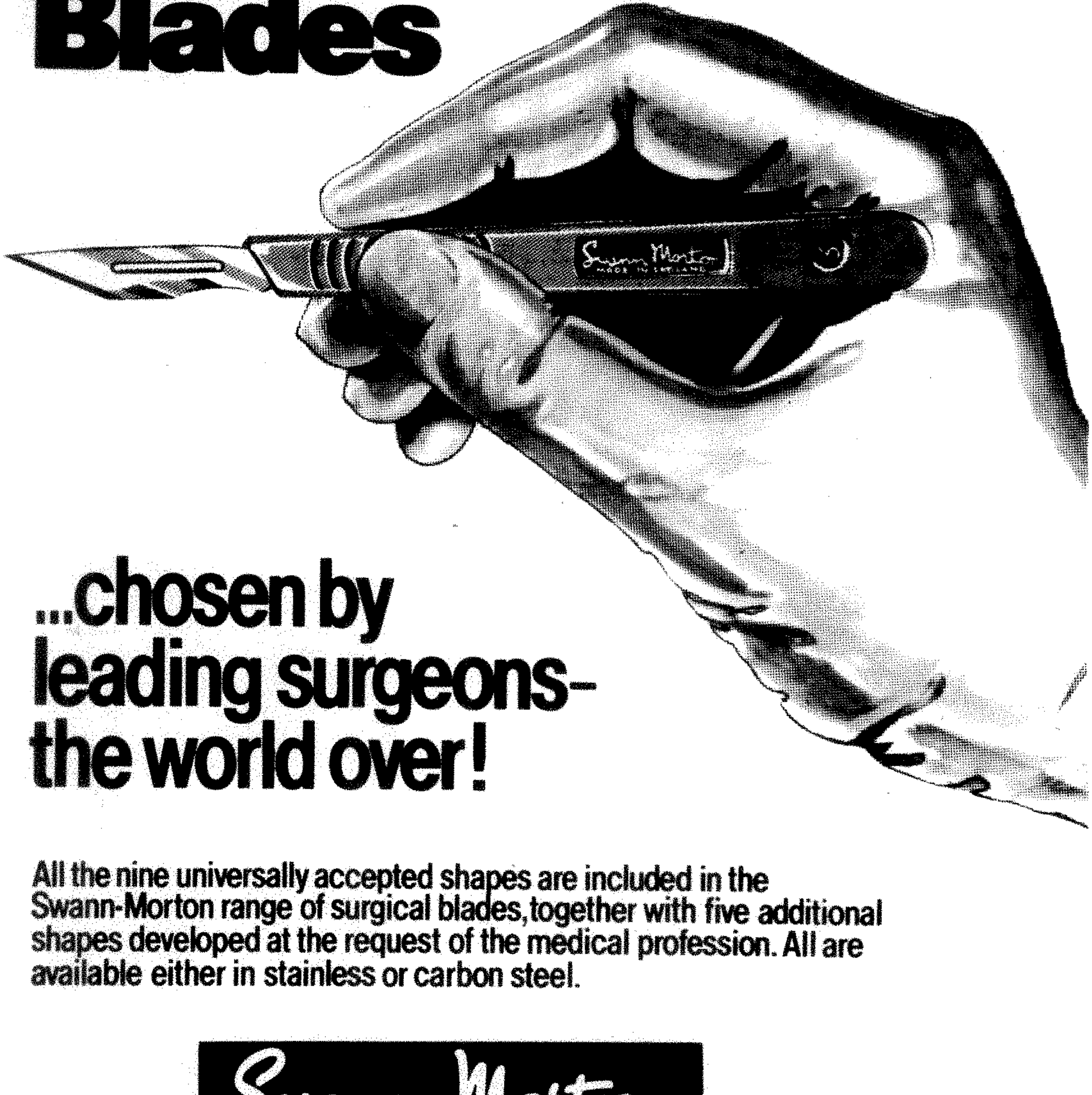

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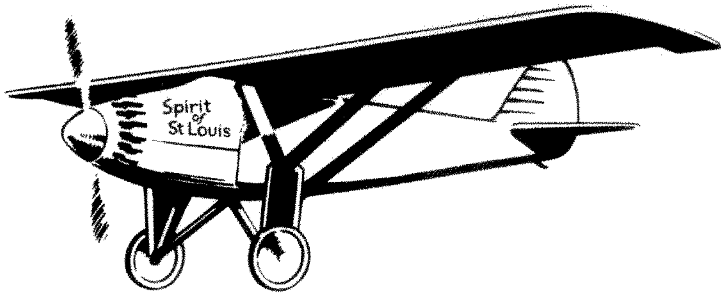

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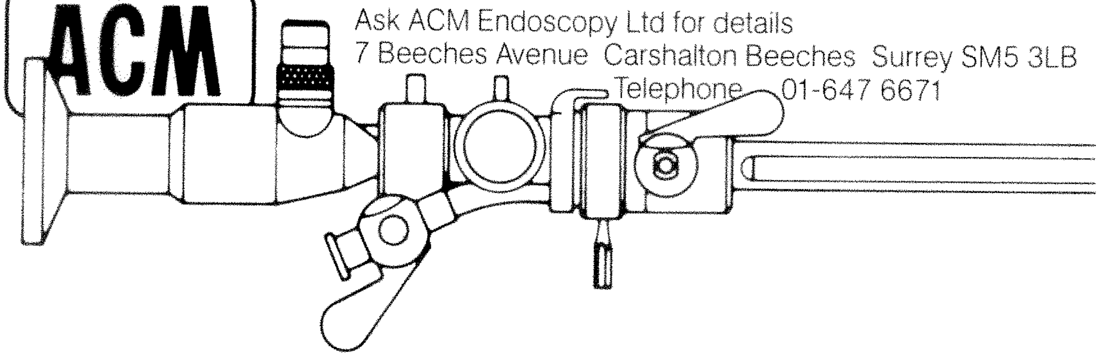

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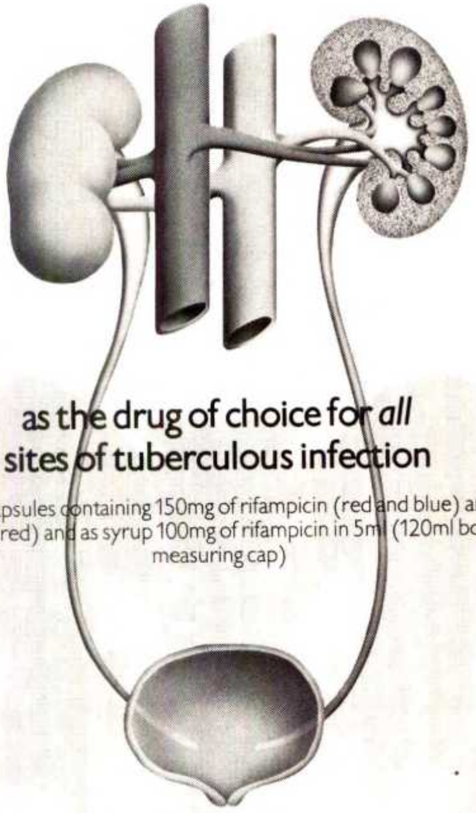

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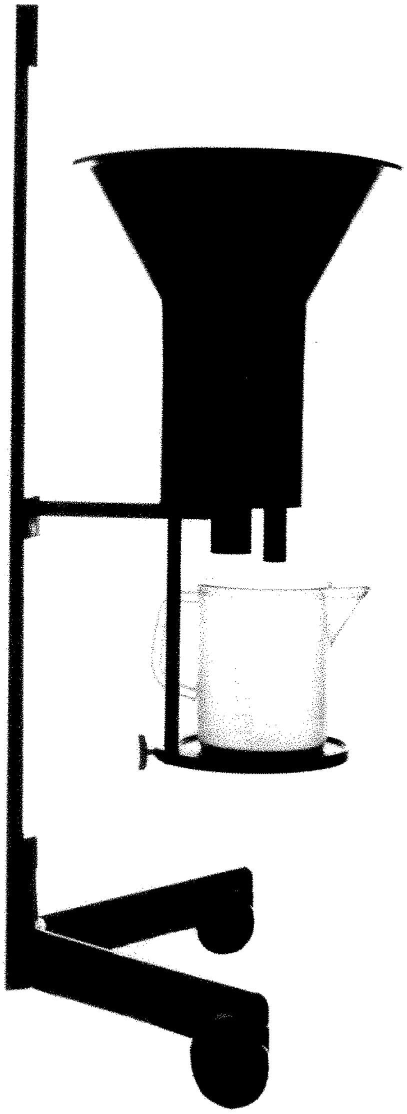

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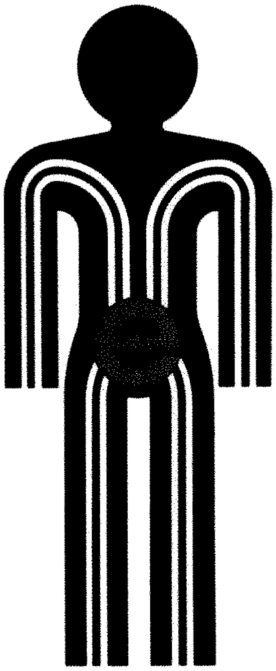

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1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer. E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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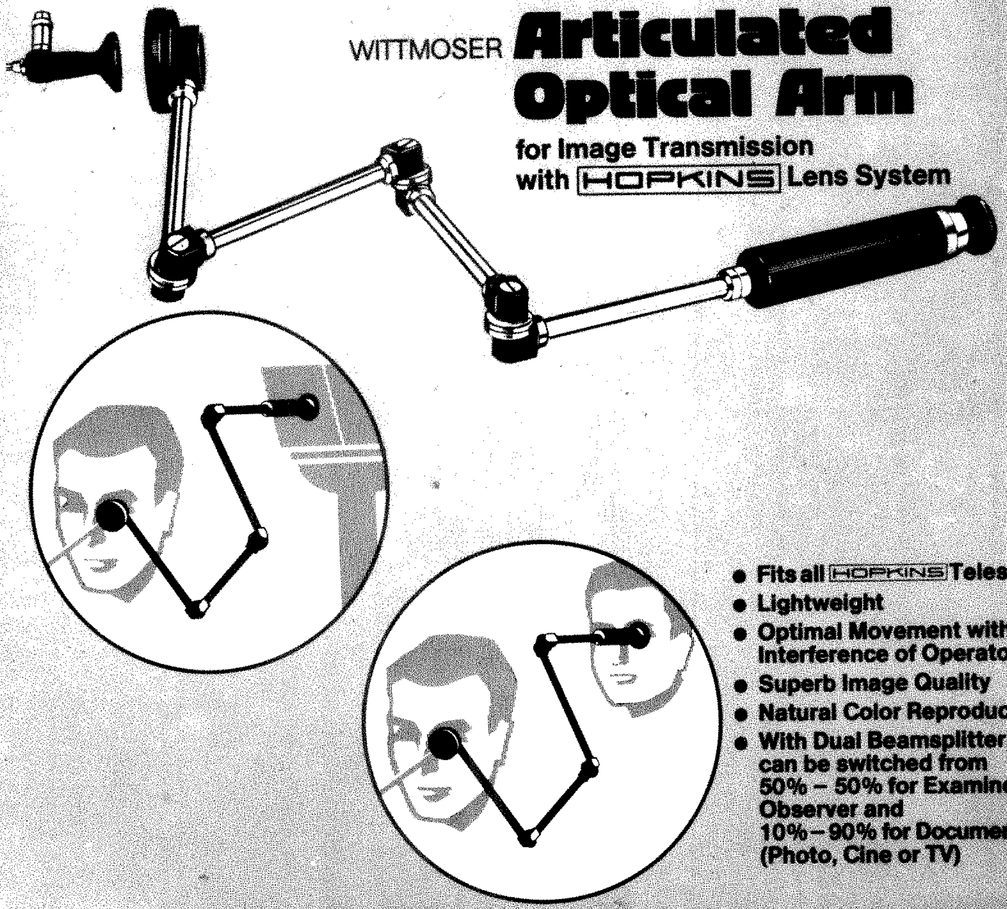

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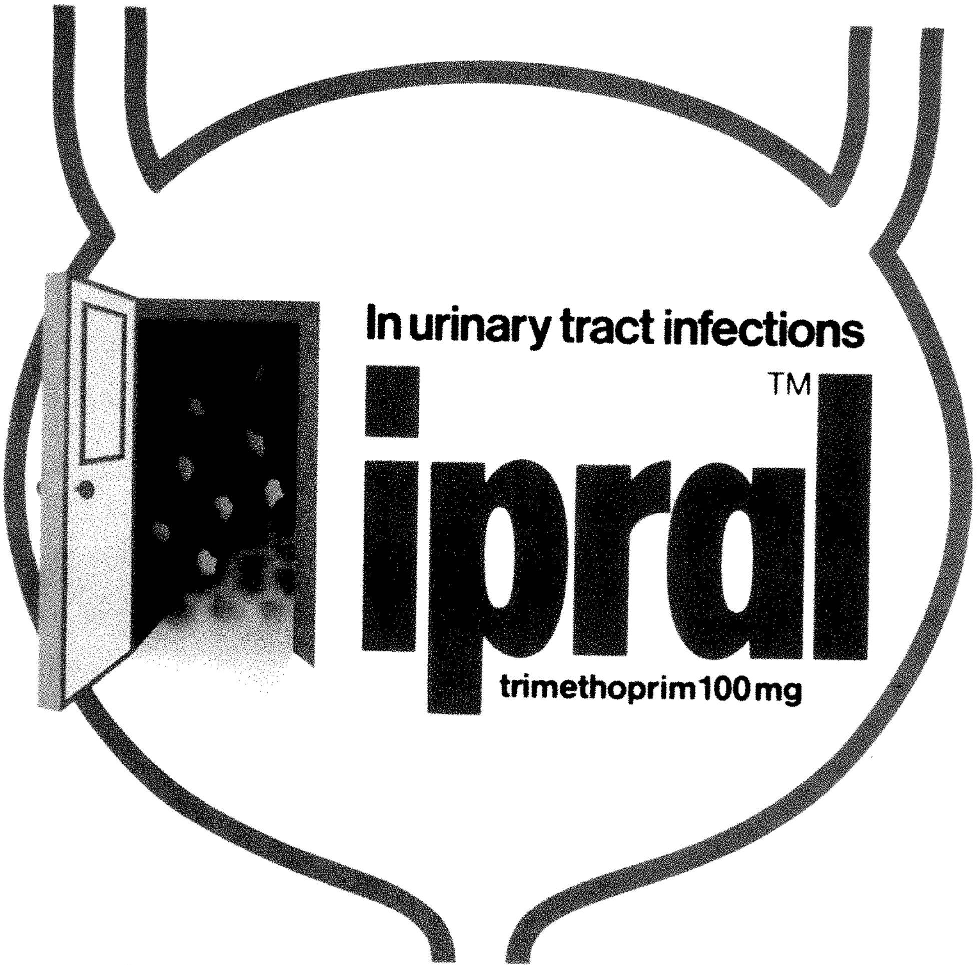

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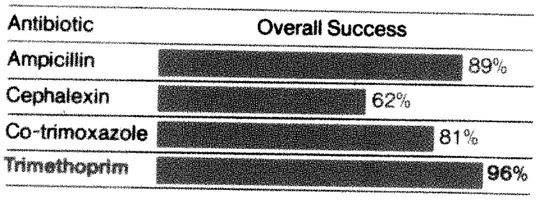

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1. Lancet 1979, **1**, 493. 2. Br. med. J. 1972, **2**, 673.
3. Ann. clin. Res. 1978, **10**, (suppl. 22). 4. Chemother. 1973, **19**, 314.

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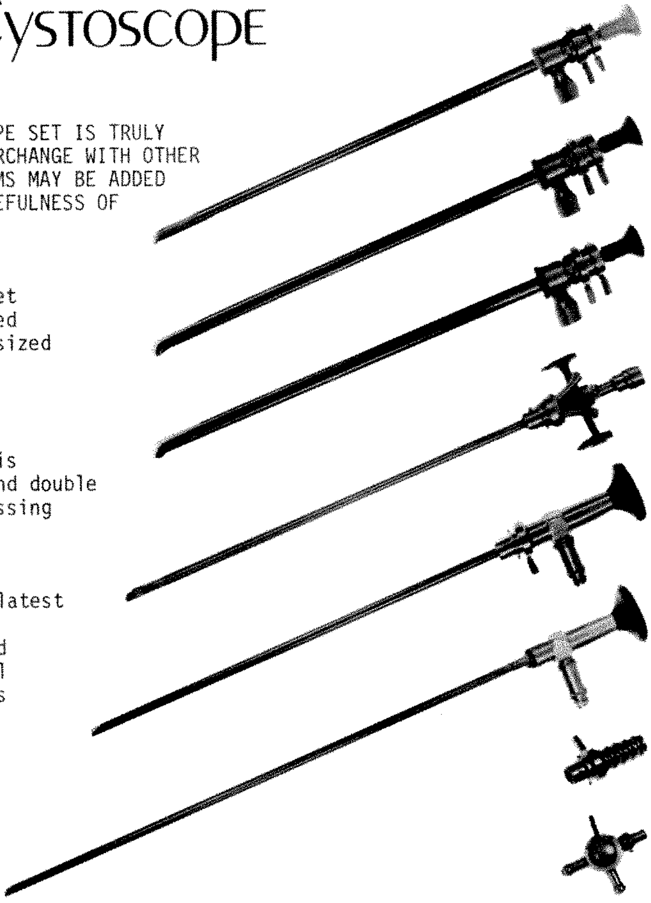

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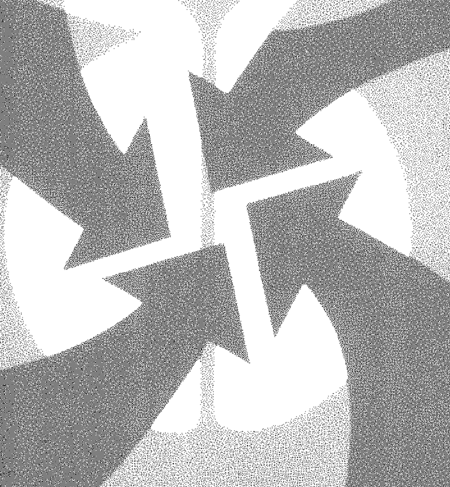

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Intrarenal Access: Effects on Renal Function and Morphology

J. M. FITZPATRICK, M. W. SLEIGHT, A. BRAACK, M. MARBERGER and J. E. A. WICKHAM

Institute of Urology and Department of Urology, St Bartholomew's Hospital, London and Department of Urology, University Hospital, Mainz, West Germany

Summary—This study describes the effect of the 4 most commonly used methods of intrarenal access on renal function and morphology in the dog at 48 h. The extended sinus approach was associated with no functional or parenchymal loss; the radial paravascular approach was followed by a 20% decrease in function and no significant parenchymal loss; the anatrophic intersegmental nephrotomy caused a 30% functional decrease with a significant parenchymal loss; the bivalve nephrotomy was associated with a 50% loss of function and considerable parenchymal loss and distortion.

As surgical techniques have improved, the complications associated with the removal of large branched renal stones have become less common. The introduction of the sinus approach to the renal pelvis (Gil-Vernet, 1965) has meant that many staghorn calculi can be removed by extended pyelolithotomy. This approach may be inadequate for the removal of intracaliceal fragments in some cases, and an incision into the renal parenchyma becomes necessary.

To minimise blood loss and improve operative vascularisation, the renal artery may be occluded when a nephrotomy is performed. The use of hypothermia (Wickham *et al.*, 1967), inosine (Fernando *et al.*, 1976; Wickham *et al.*, 1979) or magnesium chloride-ATP (Lytton *et al.*, 1979) can prevent permanent ischaemic damage in this situation. The loss of functioning renal parenchyma caused by the incision itself has not received a great deal of attention, although Maddern (1967) has shown that bivalve nephrotomy is associated with a considerable decrease in function. Other less traumatic procedures for removing stones have more recently been introduced, and the effects on function of these methods have not been compared.

The purpose of this study was to assess the effect on renal function and morphology of the extended sinus, radial paravascular, anatrophic and bivalve methods of intrarenal access.

Materials and Methods

The operative procedures described by Gil-Vernet (1965), Marshall *et al.* (1965), Boyce and Elkins (1974) and Wickham *et al.* (1974) were performed on 4 groups of 4 mongrel dogs (weighing 18 to 25 kg). Each animal was anaesthetised with sodium pentothal 30 mg/kg, intubated and allowed to breathe room air. An infusion of 500 ml normal saline was given intravenously during the operation, which was performed in each case on the left kidney through a subcostal incision. The right kidney was not touched and served as a control in each animal.

The Extended Sinus Approach

The plane between the renal parenchyma and renal pelvis was dissected without vascular occlusion and the parenchyma was retracted for 30 min. A pyelotomy was performed and closed with 4/0 chromic catgut.

The Radial Paravascular Approach

The renal artery was occluded for 30 min, during which time 3 radial nephrotomies (2 anterior and 1 posterior), each 2 cm in length, were made and by blunt dissection were extended to the pelvicaliceal system which was opened in each case. This was closed with 4/0 chromic catgut, as was the renal capsule, no further attempt being made at haemostasis.

The Anatrophic Intersegmental Approach

The artery to the posterior segment was first

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Results of Creatinine, Inulin and PAH Clearances (ml/min) in Each Group (mean±SD)

	Creatinine (ml/min)	*Inulin (ml/min)*	*PAH (ml/min)*
Controls	43.8±9.5	46.6±9.7	123.1±26.1
I Extended sinus	42.6±3.4	48.3±8.3	133.2±19.6
II Radial	29.5±3.9	33.3±5.1	83.4± 8.7
III Anatrophic	17.3±2.0	21.5±1.9	51.7± 2.4
IV Bivalve	14.4±5.8	16.6±2.9	32.0± 4.4

clamped and methylene blue injected into a peripheral vein in order to define the border between anterior and posterior segments. A 6 cm incision was then made into the renal capsule after clamping the main trunk of the renal artery (which remained occluded for 30 min). The incision was extended deeply by blunt dissection to the pelvicaliceal system which was then opened. This was closed with 4/0 chromic catgut, as was the renal capsule. Arcuate veins were commonly transected and these were undersewn.

The Bivalve Approach

An incision extending from superior to inferior poles was made 1 cm posterior to the lateral convex border after clamping the renal artery (which remained occluded for 30 min). It was extended deeply by blunt dissection to the pelvicaliceal system, which was subsequently closed with 4/0 chromic catgut, as was the renal capsule. Transected vessels were undersewn before closure of the renal capsule and 3 loosely tied vertical mattress sutures were inserted.

The animals were re-anaesthetised 48 h later and both ureters were transected and intubated. Clearance studies of creatinine, inulin and PAH were performed on both the experimental and control sides in all cases. At the end of the urine collections the dogs were sacrificed by an overdose of sodium pentothal. Both kidneys were then removed.

Parenchymal loss was assessed by injecting a polyester resin into the renal vascular system and then corroding the remaining tissue with hydrochloric acid. This technique was originally described by Tompsett (1970), and recently used in cadaver kidneys by Sleight *et al.* (1980).

Results

Functional Changes

The effects on creatinine, inulin and PAH clearances at 48 h in the 4 different groups are shown in Tables 1 and 2 and Figures 1 to 3. In Table 2 it can be seen that there was no significant difference in creatinine, inulin or PAH clearances between the extended sinus approach and controls; there was no significant difference in creatinine or inulin clearance between the radial approach and controls, although there was a difference in PAH clearance. There was no significant difference in creatinine and inulin clearance between the anatrophic and bivalve nephrotomies.

Figures 1 to 3 compare the clearance results in each group of operative procedures. The figures in parentheses refer to the statistical difference between that group and the previous group. There was a significant difference in the creatinine, inulin and PAH clearances between the extended sinus and the radial approach, and between the radial and anatrophic approaches. There was no significant difference in creatinine or inulin clearances between the anatrophic and bivalve incisions.

Taking the main clearance values for each

Table 2 Statistical Difference in Function between Experimental and Control Kidneys

	Clearance		
	Creatinine	*Inulin*	*PAH*
I Extended sinus	N.S.	N.S.	N.S.
II Radial	N.S.	N.S.	$P=0.01$
III Anatrophic	$P<0.05$	$P<0.001$	$P<0.001$
IV Bivalve	$P<0.01$	$P<0.002$	$P<0.01$

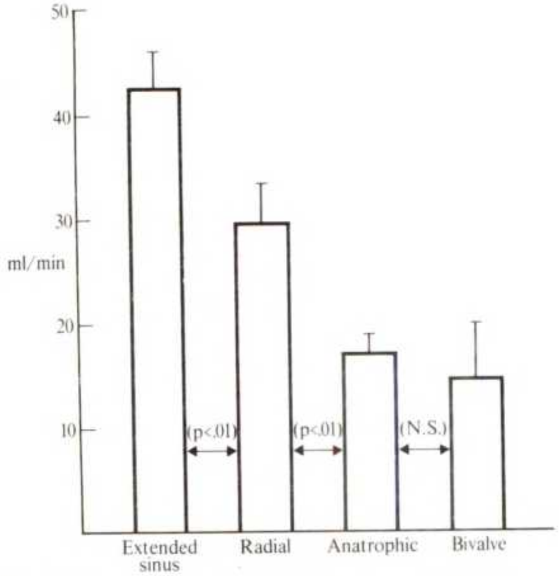

Fig. 1 Creatinine clearance in each group (mean ± SD).

operative procedure, there was no overall reduction in function at 48 h in the extended sinus group. There was a 20% reduction in function in the kidneys which had radial nephrotomies, a 30% reduction in function in the anatrophic group, and a 50% functional reduction in the kidneys which had a bivalve nephrotomy.

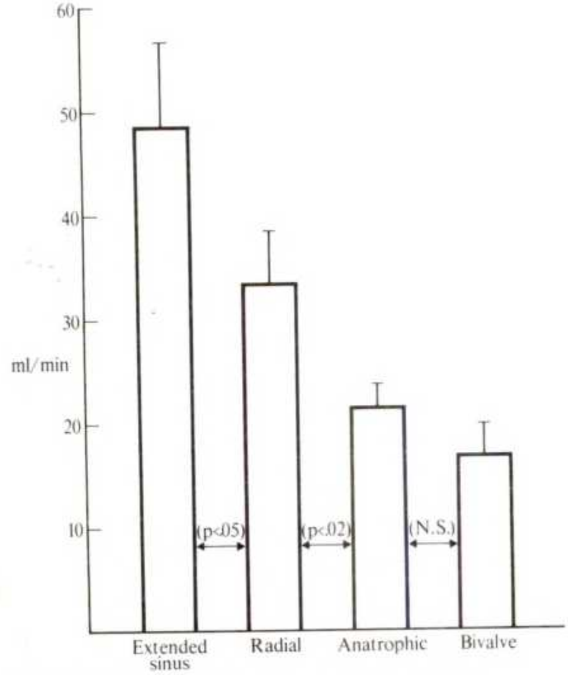

Fig. 2 Inulin clearance in each group (mean ± SD).

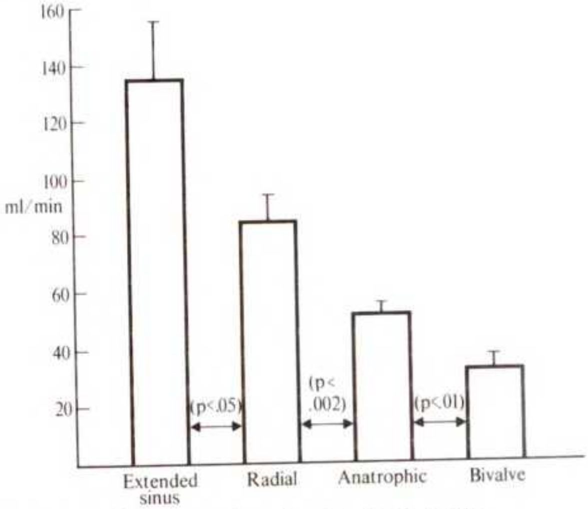

Fig. 3 PAH clearance in each group (mean ± SD).

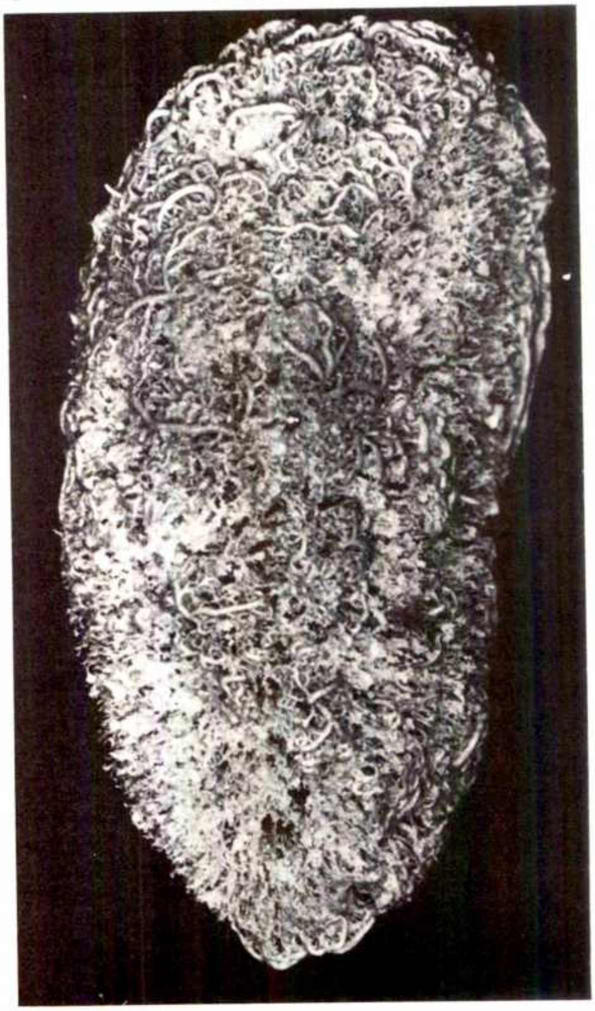

Fig. 4 Cast of kidney. Extended sinus approach.

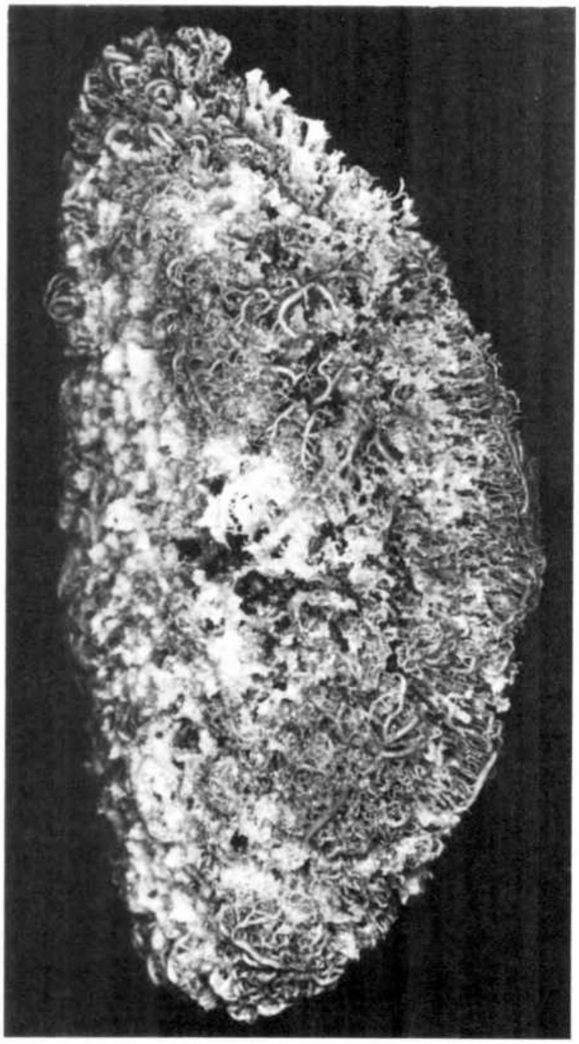

Fig. 5 Cast of kidney. Radial paravascular approach.

Morphological Changes

These are shown in Figures 4 to 7. The extended sinus and radial nephrotomies were not associated with parenchymal loss, although there was a minimal loss in one of the nephrotomies in this group. A significant trough of parenchyma was lost in the kidneys which had the anatrophic nephrotomy, with gross parenchymal loss and distortion in the bivalve group.

Discussion

There can now be little doubt that staghorn calculi should be removed because of the increased morbidity and mortality associated with leaving them behind. Blandy and Singh (1976) and Rous and Turner (1977) have reported a very high mortality (30%) in patients with conservatively managed renal calculi. Although most stones can be removed through an incision in the renal pelvis, some fragments in the calices may be inaccessible. The importance of complete removal of such fragments is also undisputed, since incomplete removal is associated with a high recurrence rate.

The need to find an incision through renal parenchyma, which combines maximum caliceal exposure with minimum functional loss, is obvious. Maddern (1967) showed that the bivalve nephrotomy caused severe damage to the pig kidney and that the sutures used for securing haemostasis were traumatic. The principle associ-

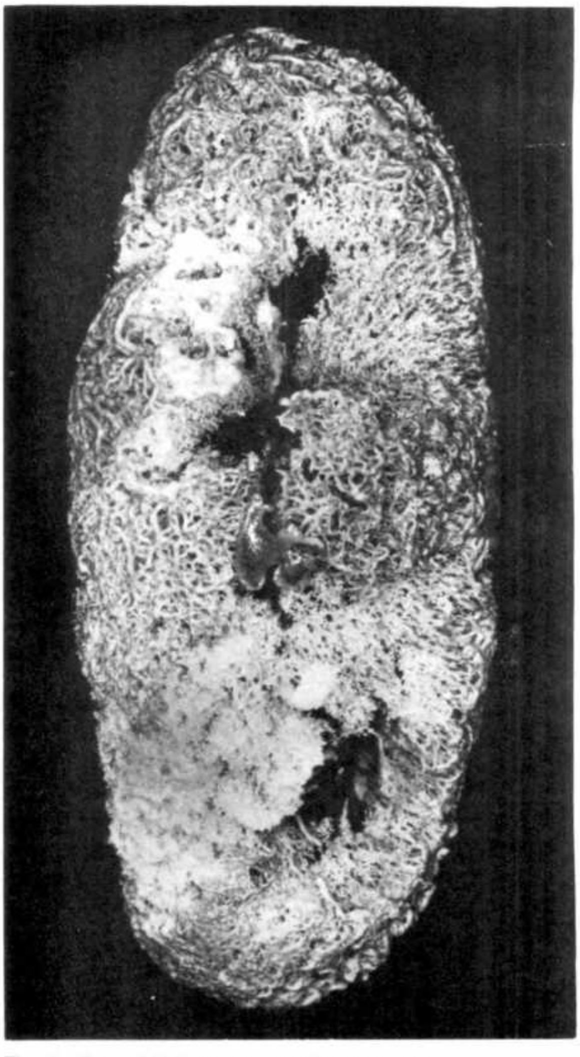

Fig. 6 Cast of kidney. Anatrophic approach.

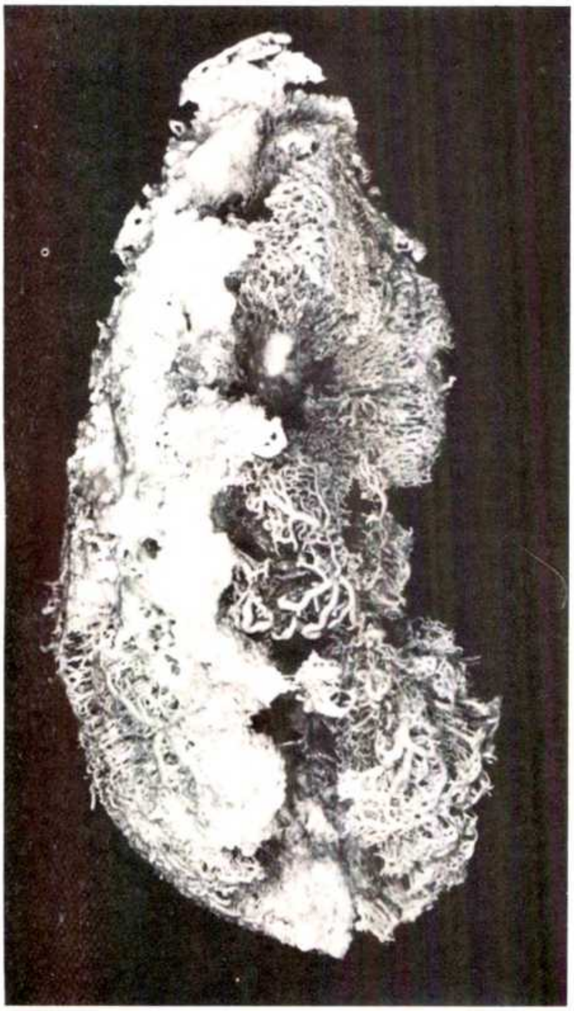

Fig. 7 Cast of kidney. Bivalve approach.

ated with the bivalve operation is that the incision is made on Brödel's "bloodless line", combining avascularity with good exposure. In their review of 50 cases of bivalve nephrolithotomy, however, Marshall *et al.* (1965) were unable to find this "bloodless line" in any case, and numerous significant vessels were transected. They reported a 32% decrease in function post-operatively, and this marked decrease has been confirmed by Marberger (1979). Taguchi *et al.* (1980) noted that one-layer interrupted sutures, from cortex to pelvicaliceal system, did not cause such renal damage, but their results showed a 20% decrease in *total* glomerular filtration rate (GFR) in the first week. They did not test the pre-operative GFR in the kidney to be operated on, so that the effect on kidney function was unclear.

Smith and Boyce (1968) and later Boyce and Elkins (1974), using anatomical principles, pointed out that the avascular line was in fact the line between the anterior and posterior renal segments. It was clear that this could not be found by a blind incision into the renal parenchyma, but only by defining carefully the intersegmental line by occluding the posterior segmental branch of the renal artery and injecting methylene blue dye. The incision would then be extended towards the necks of the calices and combined if necessary with calicoplasty. Once again, the claim was made for an incision which combined minimal arterial transection with maximum exposure. Smith and Boyce (1968) reported a decrease in renal function in 6% of their series using radioisotope studies, and Boyce and Elkins reported no decrease in renal function using the blood urea nitrogen as their index of renal damage. Stubbs *et al.* (1978) found that the serum creatinine remained unchanged following anatrophic nephrolithotomy in single kidneys. In none of these studies was it stated when renal function was assessed, and so the immediate effect of the anatrophic nephrolithotomy remains uncertain.

The main emphasis has been on avoidance of arterial transection, the occurrence of venous damage being considered unimportant. Sleight *et al.* (1980) observed that the veins *are* important because of excessive back-bleeding during the operation if they are cut, and undersewing them to prevent post-operative haemorrhage is a further cause of renal damage. The anatrophic nephrotomy is aimed directly at the venous anastomoses at the necks of the calices, and considerable venous haemorrhage occurs if these vessels are not sutured.

The radial paravascular incision is placed high on the renal cortex close to the convexity of the kidney. The capsular incision is extended by blunt dissection in order to sweep the vessels out of the way, towards the renal papilla, which is the least vascular part of the kidney. Wickham *et al.* (1974) and Sleight and Wickham (1977) found a negligible effect on renal function associated with multiple radial incisions when removing large branched stones. It appears to be the method of choice when a parenchymal incision is necessary.

This study shows that there is no functional loss associated with the extended sinus approach. Radial nephrotomies caused the least functional or parenchymal loss, whereas there appeared to be a significant loss of function and renal parenchyma with the anatrophic and bivalve incisions. It is suggested that staghorn calculi are best removed by the extended sinus approach, using adjuvant radial nephrotomies for the removal of intracaliceal fragments.

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Hypothermic Nephrolithotomy in Solitary Kidneys

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Summary—The functional effects of nephrolithotomy performed with ischaemia and cooling have been studied in a series of 29 operations performed on patients with a solitary kidney.

There was temporary post-operative functional deterioration in every patient, but this was followed by rapid and satisfactory recovery, often with functional improvement, in 27 out of the 29 cases. Only 2 patients showed minor functional deterioration, but both benefited clinically from their surgery and remain well. No patient required permanent dialysis support.

A previous study by Wickham (1979) has shown satisfactory results from 250 cases of nephrolithotomy performed with ischaemia and cooling, but in these cases it was not possible to assess the degree of compensation provided by the non-operated kidney. The study of patients undergoing surgery to solitary kidneys obviates the question of contralateral functional compensation.

Patients and Methods

Ischaemic nephrolithotomy with hypothermic protection was performed on 29 solitary kidneys in 26 patients, 3 of whom required a second operation for calculus recurrence at 3½, 5½ and 6 years respectively. The reasons for the absence of the contralateral kidneys are listed in Table 1.

Stone composition was recorded in 23 cases. Eighteen of these were triple phosphate, 2 were calcium phosphate and there was one each of calcium oxalate, cysteine and uric acid. Stone culture revealed *Proteus* infection in 17 cases, *Esch. coli* in 2 and staphylococci in 2. Eight stones were non-infected.

Most of the patients complained of loin pain as their major symptom; the remainder had symptoms attributable to recurrent urinary tract infection.

The operative technique used was that described by Wickham *et al.* (1974), namely occlusion of the renal artery followed by the circulation of iced water through heat exchanger coils placed on either side of the kidney until a core temperature of 20°C had been reached. Calculi were removed by a combination of extended pyelolithotomy with multiple radial paravascular nephrotomies.

Renal function was recorded by pre-operative and regular post-operative serum levels of creatinine and urea, and creatinine clearance levels were used when available.

Table 1 Causes of Single Kidneys. (Details Known in 21 Patients)

Nephrectomy for stone disease	12
Congenital	3
Non-functioning	3
Nephrectomy for tuberculosis	2
Nephrectomy for carcinoma	1
	21

Results

Renal ischaemia times are shown in Table 2, the mean duration being 64 min.

The patients were divided into 2 main groups, based on their pre-operative serum creatinine levels. Those in whom this level was less than 150 μmol/l were designated Group A, and those with a level greater than 150 μmol/l were Group B. Those few patients requiring post-operative dialysis support fell naturally into the latter group. Changes in renal function in patients from the 2 groups are shown in Figures 1 and 2.

Following surgery, all patients showed an initial deterioration in renal function. In the majority this reached its maximum between 48 and 72 h and in all cases occurred before the end of the fifth day.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Times of Renal Ischaemia. (Details Known in 26 Patients)

<45 min	4 cases
46-70 min	11 cases
71-90 min	10 cases
>90 min	1 case
Mean ischaemia time—64 min (range 18-98 min)	

Table 3 Results in Group A: Patients with Pre-operative Creatinine <150 μmol/l

Satisfactory return to this level		15
Within 2 weeks	10	
Between 2-3 weeks	4	
Longer	1	
Patients with deteriorated function		1
		16

Group A—Normal Pre-operative Function (Table 3)

This group comprised 16 of the 29 cases. One patient showed some deterioration in function to a creatinine level of 250 μmol/l, having undergone re-exploration for renal bleeding post-operatively.

Follow-up of this group (25 months mean) showed that stable renal function was maintained by 14 of the 16 patients. One patient went on to improve his creatinine clearance by 20 ml/min. One patient showed slight deterioration to 190 μmol/l creatinine at 4 years, presumably not a direct result of operative cooling and ischaemia.

Group B—Depressed Pre-operative Function (Table 4)

The remaining 13 patients fell into this group. Seven of these patients showed significant functional improvement following their surgery, 5 having attained serum creatinine levels of less than 150 μmol/l. One patient only showed some functional deterioration, with a serum creatinine of 270 μmol/l compared with 180 μmol/l pre-operatively.

Ten of the 13 patients in this group maintained stable renal function on follow-up (28 months mean). Two patients re-formed calculi and required further surgery. The one patient who showed some functional deterioration post-operatively continues to improve towards his pre-operative level after one year.

Dialysis

Pre-operative haemodialysis was required by 2 patients in Group B, both of whom needed one dialysis post-operatively. Both patients regained serum creatinine levels of under 150 μmol/l. One of these patients re-formed calculi and underwent further surgery, following which 2 dialyses

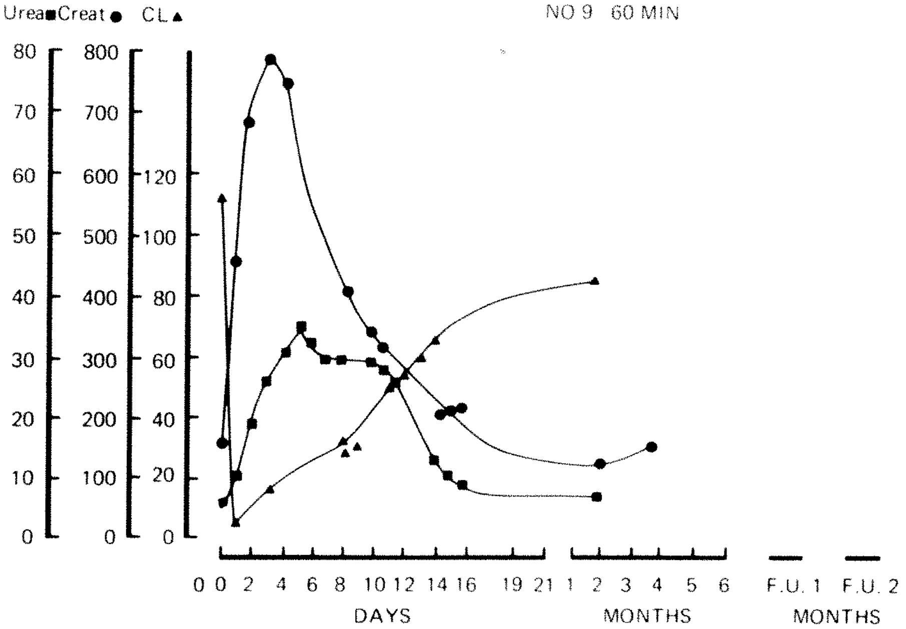

Fig. 1 Biochemical observations following hypothermic nephrolithotomy in a patient with normal pre-operative function.

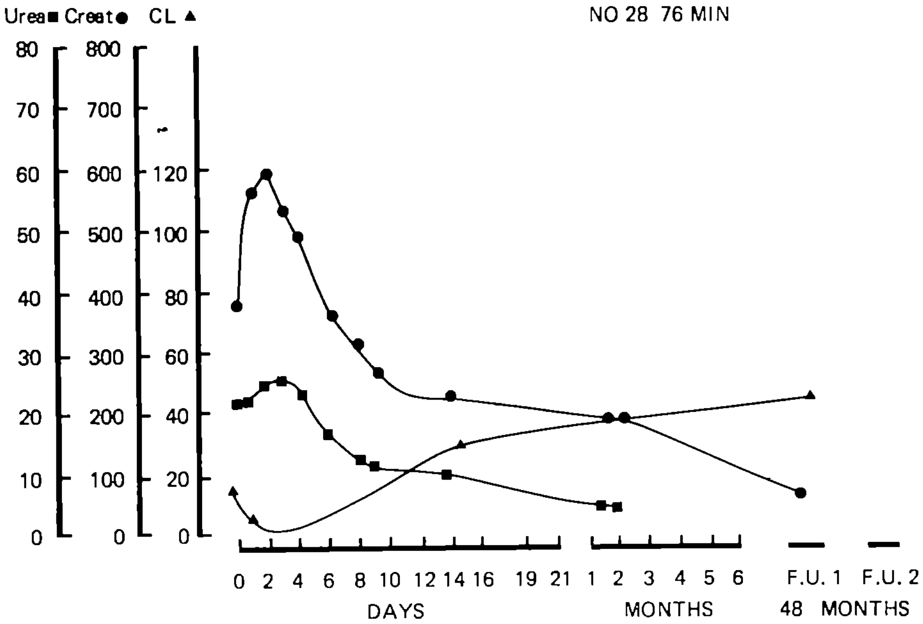

Fig. 2. A patient with depressed pre-operative function.

were required (Fig. 3). Again there was overall significant functional improvement.

Both Groups

Thus 19 of the 29 kidneys showed undiminished renal function. In addition, 8 kidneys demonstrated considerably improved function. Only 2 patients showed diminished function, but they remain clinically well and one shows continued improvement.

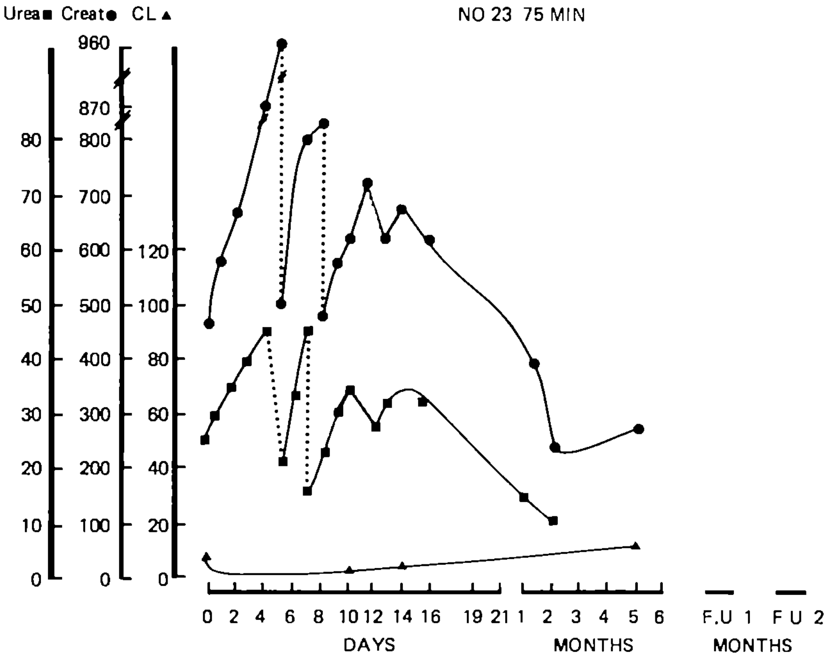

Fig. 3. A patient with post-operative dialysis support.

Table 4 Results in Group B: Patients with Pre-operative Creatinine >150 μmol/l

Patients regaining pre-op level		12
Within 2 weeks	7	
Between 2-4 weeks	4	
Longer	1	
Patients with deteriorated function		1
		13

Significantly improved function in 7 patients (<150 μmol/l in 5)

Discussion

We have shown that although there is an initial deterioration in renal function following such procedures, there will be rapid and satisfactory recovery in almost all patients. Over half of the patients with decreased pre-operative renal function showed significantly increased function at follow-up. All patients were relieved of their symptoms and remain well. There was no operative mortality and no patient was precipitated into chronic dialysis therapy. Temporary dialysis support was not indicative of a poor prognosis.

Redman and Bissada (1976) have reported satisfactory results following 2 cases of hypothermic nephrolithotomy, performed on previously operated solitary kidneys. Many of the kidneys in our series had undergone previous surgery and we agree with their findings that extensively operated kidneys should not deter salvage stone surgery in solitary kidneys. Stubbs *et al.* (1978) have also reported satisfactory function following 30 such operations on solitary kidneys.

We therefore recommend that, in addition to its proven safety in patients with 2 kidneys, ischaemic nephrolithotomy using hypothermic protection may be used safely when required, even in the presence of significant pre-operative functional impairment.

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Nephrolithotomy in Chronic Renal Failure: Saved from Dialysis!

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Summary—In patients with severely decreased renal function due to stone disease, dialysis has been suggested as an alternative to surgery.

We reviewed 19 patients with creatinine clearances of 20 ml/min or less in whom nephrolithotomy was undertaken. Mean clearances increased significantly from 12.9 to 25.4 ml/min ($P<0.01$). No patient required long-term dialysis.

Points in technique that contribute to this improvement in function are discussed.

Obstruction and pyonephrosis as a consequence of failing to operate on a staghorn calculus are well documented (Priestley and Dunn, 1949; Singh *et al.*, 1973). A neglected complication of more insidious onset is chronic renal failure, yet over half of the patients in one series which assessed the results of conservative management died in uraemia (Singh *et al.*, 1973). Despite these findings, it is our impression that when renal function is severely compromised, both surgeons and nephrologists are reluctant to advise nephrolithotomy. This view, based on Borelius' (1908) original concept of the sanctity of the renal parenchyma, has been recently reinforced in a review of the results of surgery for staghorn calculus in the solitary kidney (Stubbs *et al.*, 1978). In 3 cases, with a creatinine clearance of less than 12 ml/min, operation was not attempted and the patients were referred directly for dialysis.

We have reviewed our cases of staghorn calculi with severely compromised function, of which the majority had been referred for consideration of renal replacement therapy, either chronic dialysis or transplantation.

Patients and Methods

Nineteen patients with a creatinine clearance of 20 ml/min or less (range 4-20 ml/min) have been seen over the last 10 years in a series of over 300 patients with staghorn calculi. Their average age was 47.5 years (range 23-63 years). Eight patients had solitary kidneys, the previous nephrectomy being for stone.

Conservative renal surgery was undertaken in every case. All stones were large, branched staghorn calculi whose removal necessitated ischaemic renal surgery, with hypothermia as protection in 18 cases and inosine protection only in one of the later cases. (One patient's condition was so poor that temporary pre-operative haemodialysis was necessary.)

The usual operative technique was pyelolithotomy with multiple, paravascular dissection nephrotomies as necessary, 13 being made on one occasion to complete stone removal. The techniques of stone localisation have been previously described (Wickham and Mathur, 1971). In these cases with severely compromised renal function, our aim of complete stone removal has been tempered by the fear of compromising renal function.

Results

Twenty-one operations were performed on the 19 patients, who have been followed from 10 years to 2 months (mean 6.3 years). Renal ischaemia time varied from 18 to 90 min, with a mean of 61 min (S.D. 18 min). Inosine alone was used in one patient, with an ischaemic time of 57 min (Case 18, Table).

Stone clearance was complete in all cases but 2. In one patient (Case 5) a 6 mm fragment could not be located. In the other case the remaining fragments were all less than 2 mm, a size unlikely to cause obstruction (Case 6).

Stone analysis revealed one uric acid calculus,

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table

Case	*Age*	*Sex*	*Ischaemia (min)*	*Creatinine clearance (ml/min)*	
				Pre	*Post-op.*
1	59	F	36	4	5
2	42	F	75	7	40
3	63	F	73	9	25
4	54	M	90	9	22
5	62	M	83	10	15
6	60	F	90	10	5
7	28	M	49	11	22
8	53	F	50	12	18
9	32	F	73	12	17
10	40	M	18	12	32
11	44	F	60	14	20
12	23	M	76	15	25
13	42	F	63	16	25
14	36	F	72	19	18
15	52	M	—	20	25
16	43	F	48	20	72
17	60	F	60	20	45
				Creatinine (mmols/l)	
				Pre	*Post-op.*
18	55	M	57	0.34	0.28
19	48	M	50	0.7	0.53

one cystine and the rest to be magnesium, ammonium and phosphate secondary to infection.

Creatinine clearance pre-operatively ranged from 4 to 20 ml, with a mean of 12.9 ml/min (S.D. 4.8). In the early post-operative period the clearances were often diminished, so much so that dialysis was necessary on 3 occasions in 2 patients. Post-operative clearances ranged from 5 to 72 ml/min, with a mean of 25.4 ml/min (S.D. 15). When these values were compared with those obtained prior to operation, there was a significant increase ($t = 3.67$, $P<0.01$, Student's paired t test).

Usually function was much improved within 3 weeks of surgery, but in the severely compromised case, the maximal benefit may not be seen until over 3 months after surgery, and can improve for several years after operation. Post-operative clearances diminished in 2 cases; in one, a clearance of 19 ml/min fell to 18, and in the other, from 10 to 5 ml/min (Case 6). The latter suffered the longest ischaemic time (90 min), but follow-up is now only 3 months and further improvement may occur. Function improved in all of the remaining patients. The greatest improvement in creatinine clearance was from 7 ml/min to 42 ml/min.

Two patients were hypertensive and remained so post-operatively, both requiring treatment. One was easily controlled (Case 8), the other with difficulty (Case 1). In addition, renal function was severely impaired in the latter, being only 4 ml/min prior to surgery, with minimal improvement to 5 ml/min following operation. Her function continued to deteriorate and she died of uraemia, aged 63, 4 years following surgery. She was a poor candidate for dialysis. Another patient died 1 year following stone surgery for a squamous cell carcinoma in the contralateral, non-functioning kidney which was awaiting removal. All other patients avoided long-term dialysis, and all bar one have avoided dietary restriction, leading healthy, active lives.

Discussion

In patients with severely compromised renal function due to staghorn calculus, stone removal has resulted in a significant improvement in creatinine clearance. There is no comprehensive previous report in the literature of the results of stone surgery in the uraemic patient. Boyce and Elkins (1974), using the technique of anatrophic nephrolithotomy, reported minimal improvement in renal function as measured by blood urea in 100 cases of stone removal. In the solitary kidney (Stubbs *et al.*, 1978), stone removal by the same technique resulted in improvement in function, from a mean clearance of 52 ml/min to 55 ml/min, a result that did not reach significance. These authors referred 3 cases with creatinine clearances of less than 12 ml/min for dialysis, rather than attempt stone removal, as we would recommend. Marshall *et al.* (1965), using the bi-valve technique, reported an 18% decrease in renal function in their series. Our experience in the uraemic patient is that stone removal will improve function sufficiently to avoid dialysis.

The improvement in function that can be achieved depends on both anaesthetic and surgical expertise. Increased catecholamines, resulting from hypothermia or acidosis, increase renovascular resistance, as do ether and cyclopropane. An increase in antidiuretic hormone, secondary to opiates or inadequate analgesia, will reduce urine volume, as do increased levels of aldosterone, secondary to halothane or hypotension. Blood loss must be replaced as it occurs, and can be considerable where adhesions exist from previous surgery.

Maximal improvement in renal function is achieved by minimal interference with renal tissue. Although these calculi are generally extensive and require nephrolithotomy in addition to pyelolithotomy, renal damage can be minimised by the paravascular, dissection nephrotomy. Only the capsule and superficial cortex is incised; the calix is then displayed by blunt dissection, preserving any vessels seen en route.

Although it is always desirable to obtain complete stone removal (Wickham *et al.*, 1974), one should temper obsessive attempts at clearance of small fragments with caution in the kidney with severely damaged function. This has meant leaving small stones on 2 occasions to avoid prolonged ischaemia.

In conclusion, provided that the above precautions are observed, we consider stone clearance in the uraemic patient should be encouraged in a unit that has facilities for acute dialysis.

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Computerised Tomography Localisation of Intrarenal Calculi Prior to Nephrolithotomy

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Summary—The use of the EMI CT 5005 scanner in patients with renal calculus disease is described. This investigation was found to be a useful aid in the accurate localisation of calculi within the renal collecting system prior to surgery.

The intra-operative localisation of small peripheral renal stones within the collecting system may be the most difficult part in the operation of nephrolithotomy. The position of stones within the renal collecting system may be localised to some extent with conventional pre-operative radiography, but it is often a problem to know whether such stones lie in the anterior or posterior row of calices. Although it is easy to remove large portions of staghorn calculi by the sinus approach to the major collecting system, one may be faced with the task of locating one or more residual caliceal calculi situated in the periphery of the kidney. It may then be difficult to determine whether these lie anteriorly or posteriorly and hence whether a nephrotomy approach should be made on the anterior or posterior surface of the kidney. Gil-Vernet (1980) has used 3-dimensional intra-operative radiography to localise these stones, but this requires special forceps and X-ray cassettes.

In an attempt to resolve this problem we have studied a group of patients using pre-operative computerised tomography (CT) scanning to evaluate its role in the accurate pre-operative localisation of renal calculi

Patients and Methods

Ten patients, prior to nephrolithotomy for stone disease, were examined by the EMI CT 5005 scanner to produce transverse cuts of approximately 1 cm thickness at intervals through the renal areas. A set of graduated lengths of radioopaque angiography catheters (Fig. 1a) was taped to the patient's back across the renal area before the preliminary X-ray and CT scan. By counting these markers on the CT scan, transverse lines could be drawn across the plain X-ray film corresponding to each cut of the CT scan (Figs. 1b and c). Thus each cut of the CT scan could be easily and accurately correlated with the plain X-ray and intravenous urogram (IVU). The multiple scans were then examined and those relevant to the particular fragment of calculus were enlarged 4 times to give better visualisation.

At operation the kidneys were fully moblised through a standard loin incision. The major portions of stone were removed through the renal sinus and the renal pedicle was then occluded. Using either regional renal hypothermia (Wickham *et al.*, 1974) or inosine functional protection (Wickham *et al.*, 1978), the peripheral portions of the stone were approached.

The standard practice was to enclose the kidney in a Netelast gauze sling to which liga-clips were then attached as markers. A lateral contact X-ray of the kidney was then taken. This was displayed on the operating theatre X-ray screen together with the appropriate CT scans, plain X-ray and IVU film. In this way a 3-dimensional localisation of the stones was obtained. It was then easy to determine if a calculus lay in an anterior or posterior calix and at what level in the kidney. Even though no stone could be palpated, a small dissection nephrotomy could be made over the area indicated and the stone removed.

Results

We have successfully removed fragments of stone from 9 patients subjected to this technique. One patient had a nephrectomy when, at operation, she was found to have a xanthogranulomatous pyelonephritis (Fig. 2).

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

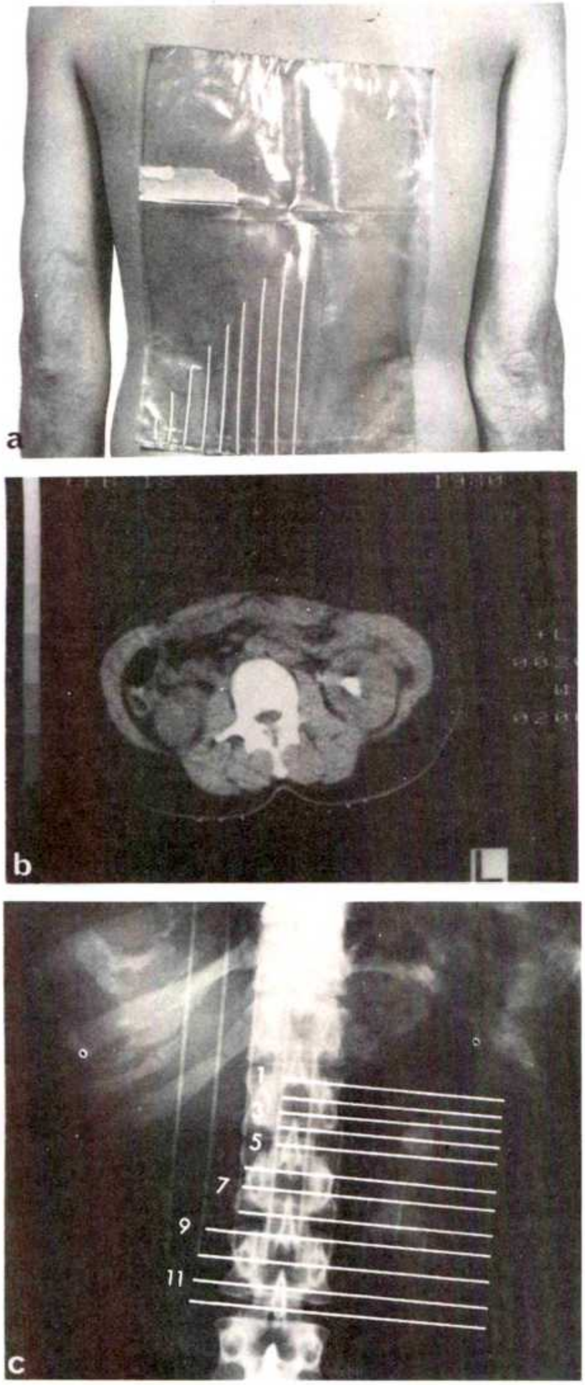

Fig. 1 (*a*) Graduated lengths of radio-opaque angiography catheters are placed on the patient's back for the preliminary X-ray film and CT scan so that the level of the CT scan can be correlated with the plain film. (*b*) The radio-opaque angiography catheters may be counted on the CT scan to give the level of the scan. (*c*) The plain X-ray with the horizontal lines drawn through the kidney at levels corresponding to each cut of the CT scan.

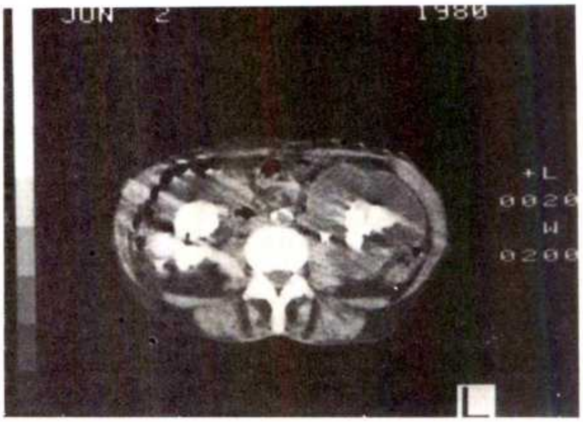

Fig. 2 Right staghorn calculus in a xanthogranulomatous pyelonephritic kidney. Note marked increase of radiolucent fat in and around the kidney.

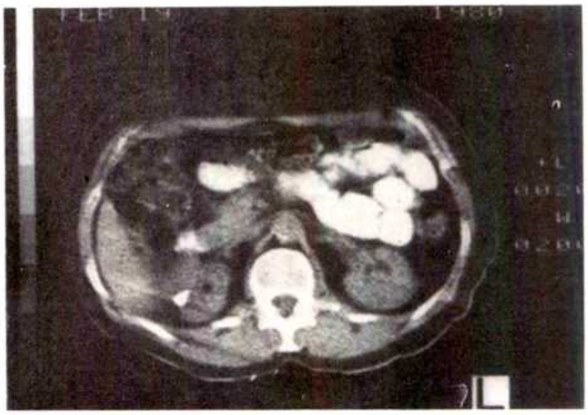

Fig. 3 A peripheral calculus localised to an anterior calix (*cf.* Fig. 4).

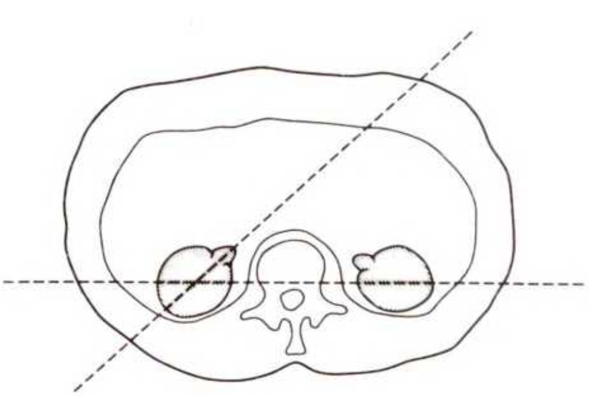

Fig. 4 The interpretation problem: radiologist *v.* surgeon. A stone lying behind the coronal plane may be in an anterior calix when the kidney is mobilised during surgery.

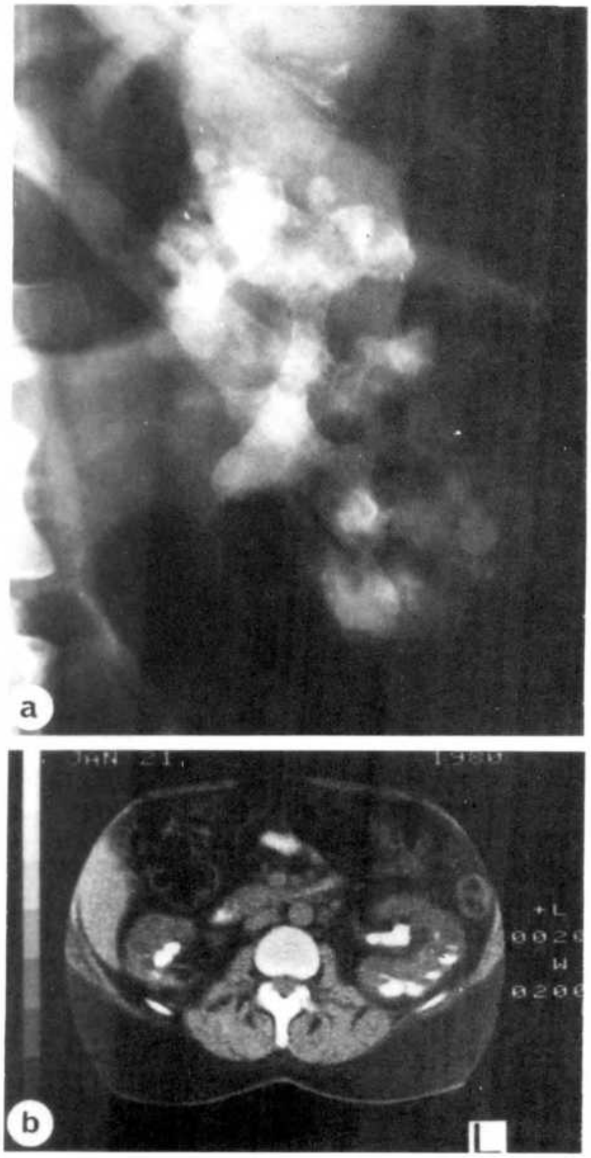

Fig. 5 (*a*) A large staghorn calculus with multiple peripheral calculi which will require multiple dissection nephrotomies. (*b*) CT scan of Figure 2 showing that all of the peripheral calculi are lying posteriorly.

The principal advantages of pre-operative CT scanning were found to be:

1. A peripheral stone could be localised to the anterior or posterior caliceal series (Figs. 3 and 5b).
2. The direction of caliceal extensions of staghorn calculi could be determined. This was helpful in the mobilisation and rotation of large conjoined caliceal and pelvic fragments of stone out of the collecting system (Figs. 5a and b).
3. The parenchymal thickness overlying calculi was easily demonstrated (Figs. 3 and 6).
4. Stones of low radio-density that were poorly visualised on plain X-rays were much more clearly demonstrated and localised on the CT scan (Figs. 7a and b, 8a and b).
5. Residual calculi on the post-operative film could be differentiated from fragments of calculi lying outside the kidney in the perirenal fat.

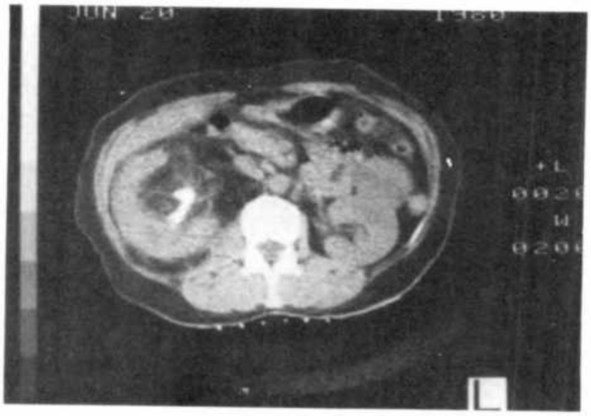

Fig. 6 The "shell nephrogram" is shown in the left kidney which showed no excretion on intravenous urography.

Discussion

The results of surgery for renal calculi depend on the complete clearance of calculi with a minimum of renal damage. For this to be accomplished incisions into the renal parenchyma may have to be made, especially with large branched staghorn calculi and peripheral calculi. Using the paravascular approach and blunt dissection through the parenchyma the damage may be minimised. However, it is essential that the incision is accurately placed over the calculus to be extracted. We have found in this series of patients that pre-operative renal CT scanning was of assistance in the operative localisation of renal calculi.

The CT scan and X-rays gave the surgeon a 3-dimensional map which could be related to the fully mobilised kidney in which the hilum and upper and lower poles were the only precise landmarks. The CT scan showed the angle that the kidney made with the coronal plane (Fig. 4). During mobilisation the kidney would be rotated through this angle and this rotation could cause

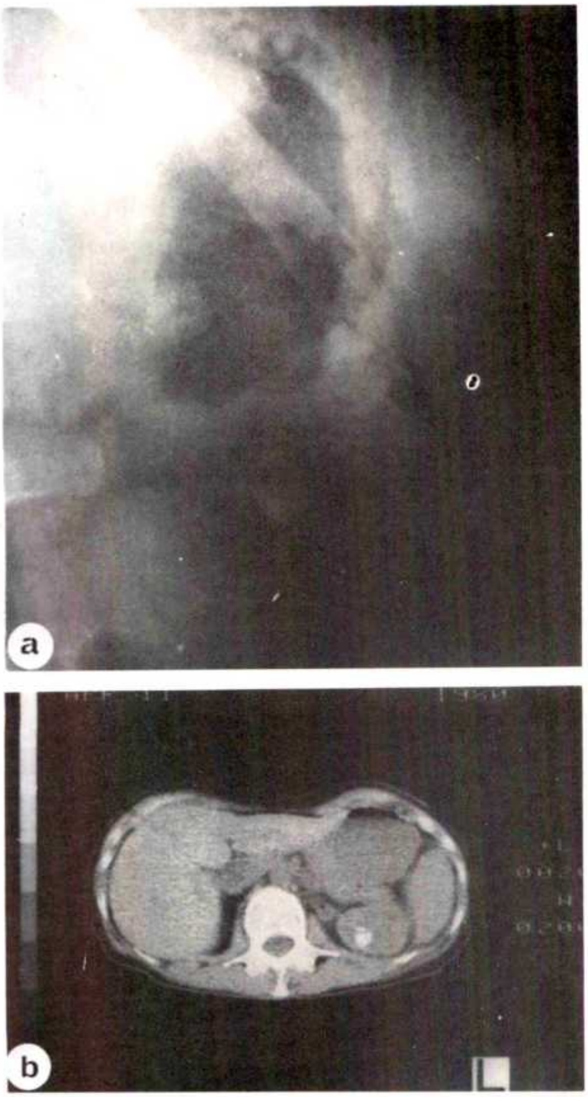

Fig. 7 (*a*) Plain X-ray showing 2 calculi of low radio-density in the left kidney. (*b*) CT scan through the upper pole of the left kidney of the same case as Figure 7a clearly showing the upper stone lying posteriorly. The lower stone was also demonstrated in lower cuts lying anteriolaterally.

confusion with the interpretation of the 3-dimensional map unless the landmarks were clearly established.

Pre-operative CT scanning adds nothing to patient morbidity but may be criticised because of the cost. The revenue cost is approximately the same as a standard intravenous urogram series. We feel that the increased speed and accuracy of operative localisation of renal stones justifies the use of this procedure.

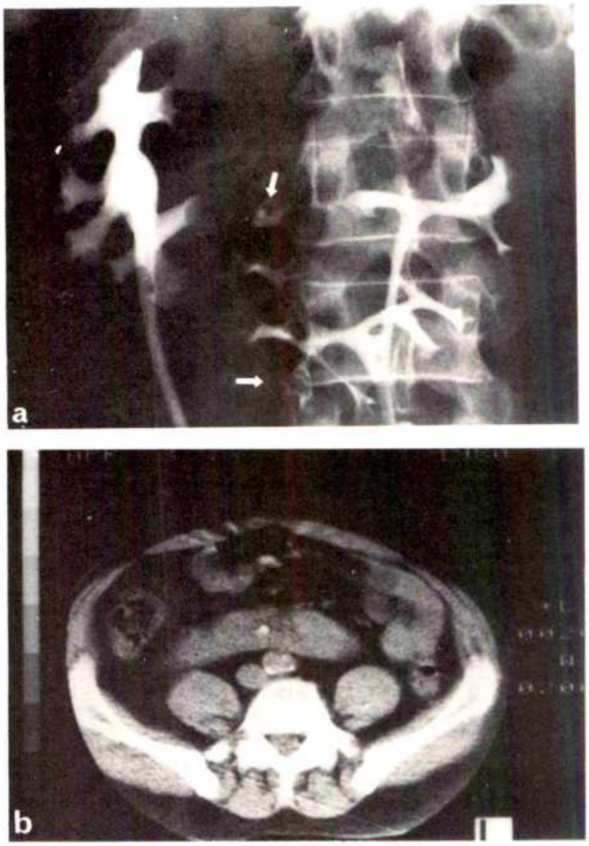

Fig. 8 (*a*) A retrograde pyelogram of a patient who was found to have microscopic haematuria. The low radio-density calculi were not demonstrated on the plain film but showed as filling defects on 2 retrograde films. (*b*) A CT scan of the horseshoe kidney shown in Figure 8a demonstrates the 2 calculi.

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Idiopathic Hypercalciuria: its Control with Unprocessed Bran

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Summary—Eighty-four patients with idiopathic hypercalciuria were entered into a study of the effects of treatment with unprocessed bran. Of 72 patients with complete data available for analysis 62 (86%) had a significant reduction in urinary calcium excretion during bran treatment and 28 (39%) returned their calcium excretion to within the normal range.

Unprocessed bran is therefore an effective means of reducing urinary calcium excretion in patients with idiopathic hypercalciuria.

The relationship between urinary calculus formation and abnormal urinary constituents has been suspected for many years. In Norfolk, where a high incidence of stone disease was present for centuries, Cadge in 1874 suspected that excess "lithic acid" was a cause of urinary calculi. Experimental evidence for the relationship between urinary calculi and a high level of urinary crystalloids was reported by Keyser in 1923. The relationship between a high urinary calcium excretion and urolithiasis was reported by Flocks (1939) and the term idiopathic hypercalciuria later used by Albright *et al.* (1953).

Idiopathic hypercalciuria occurs in approximately 50 to 60% of patients with urolithiasis (Rose and Harrison, 1974). It has been shown that if urinary calcium excretion can be reduced in these patients and maintained near normal levels (males 2.5-7.5 mmol/24 h: females 2.5-6.5 mmol/24 h), then the incidence of stone formation can be reduced (Blacklock and Macleod, 1974).

A high fluid intake and restriction of dietary calcium intake should be advised in all patients with hypercalciuria. However, restriction of dietary calcium intake over long periods is difficult to maintain and the long-term results of such restriction are not encouraging (Baker and Mallinson, 1979).

Both sodium cellulose phosphate and thiazide diuretics have been shown to be effective means of reducing urinary calcium excretion in hypercalciuric patients and the incidence of recurrent stone formation (Blacklock and Macleod, 1974; Pak *et al.*, 1974; Rose and Harrison, 1974). Long-term treatment with these agents may be associated with side effects (Rose and Harrison, 1974) and treatment is expensive.

The ideal therapeutic agent for the treatment of patients with idiopathic hypercalciuria, many of whom will not develop further stone recurrence, is one which is easily taken, inexpensive, free from side effects and requires little medical supervision.

The effect of dietary fibre on urinary calcium excretion has been reported on several occasions. Widdowson (1969) showed that a change from a diet containing white bread to wholemeal bread resulted in a reduction in urinary calcium excretion. Heaton and Pomare (1974) noted a lowering of urinary calcium excretion in patients on a high bran diet. They felt that this effect was due to precipitation in the intestine of dietary calcium with phytic acid to form the insoluble salt calcium phytate which is then excreted. Henneman *et al.* (1958) showed that a significant reduction in urinary calcium excretion could be produced in patients with idiopathic hypercalciuria when treated with sodium phytate. The dose they used, however, was large (8 g daily) and diarrhoea occurred in the majority of patients. Sodium phytate is not readily available and is very expensive.

Following an encouraging preliminary study of the effect of unprocessed bran on urinary calcium excretion in 30 patients with idiopathic hypercalciuria, a total of 84 patients have now been treated with unprocessed bran and its effect on urinary calcium excretion is reported.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Results of Treatment of 72 Patients with Idiopathic Hypercalciuria with Unprocessed Bran

Mean values	*Pre-trial*	*After 1 month's treatment*	*After 2 months' treatment*	*1 month after treatment stopped*	
Serum (mmol/1)					
Calcium	2.38	2.37	2.38	2.37	N.S.
Phosphate	0.91	0.87	0.87	0.83	N.S.
Magnesium	0.76	0.78	0.73	0.74	N.S.
Urine (mmol/24 h)					
Calcium	10.8	8.9	8.5	10.4	$P<0.001$
Phosphate	38.2	36.9	37.5	38.3	N.S.
Magnesium	4.8	4.5	4.7	4.9	N.S.
Sodium	206.0	191.0	197.0	203.0	N.S.

Patients and Methods

All patients with hypercalciuria were considered for inclusion in the study. Primary hyperparathyroidism and the other rarer causes of hypercalciuria were excluded, so that 84 patients with idiopathic hypercalciuria (2 consecutive raised 24-h urinary calcium levels, normal range 2.5-7.5 mmol/24 h) remained in the study. Patients were advised to continue on a normal diet throughout the study and no attempt was made to restrict dietary calcium intake.

Investigations prior to treatment included serum calcium, corrected calcium, phosphate, urea, creatinine, alkaline phosphatase and urate and 24-h urinary calcium, phosphate, urea, urate, creatinine and magnesium.

Patients were prescribed 24 g of fine unprocessed bran daily to be taken in divided amounts with meals for a period of 2 months. Serum and 24-h urine investigations were repeated at monthly intervals during treatment and again after treatment had been stopped for one month.

Results

Eighty-four patients were included in the study; 2 patients withdrew because they found the fine unprocessed bran unpalatable. In one patient urinary calcium levels returned to normal prior to treatment. Complete data for analysis were available in 72 patients.

The patients were aged between 21 and 65 years

Table 2 Results of Treatment with Unprocessed Bran of 72 Patients with Idiopathic Hypercalciuria (24-h Urine Values mmol/24 h)

		Before treatment	*At 1 month*	*At 2 months*	*1 month after treatment stopped*
Responding patients n = 62					
24-h urine mmol/24 h	Calcium	10.7± 2.2	8.5± 2.5	8.3± 1.8*	9.8± 2.9
	Phosphate	38.2± 9.7	36.3± 9.0	36.6± 8.5	36.2± 7.9
	Phosphate	38.2± 9.7	36.3± 9.0	36.6± 8.5	36.2± 7.9
	Magnesium	4.7± 1.4	4.4± 1.5	4.5± 1.4	4.7± 1.4
	Sodium	204.0±56.0	186.0±48.0	198.0±67.0	192.0±55.0
Non-responding patients n = 10					
24-h urine mmol/24 h	Calcium	11.2± 1.9	12.6± 2.4	12.0± 1.6	12.4± 2.5
	Phosphate	38.8±13.0	41.6± 9.9	43.7±11.9†	43.3± 9.6
	Magnesium	4.7± 1.4	5.2± 1.0	5.4± 1.5†	5.1± 1.4
	Sodium	206.0±49.0	228.0±57.0	193.0±58.0	225.0±40.0

*$P<0.001$ †N.S.

(average 41.3 years). There were 5 female patients.

The biochemical results are shown in Table 1. All serum investigations were within the normal range. Serum phosphorus was towards the lower limit of normal, as is usually seen in patients with idiopathic hypercalciuria (Rose and Harrison, 1974). The mean pre-trial urinary calcium excretion was 10.8 mmol/24 h. The mean urinary magnesium excretion was 4.8 mmol/24 h, which is towards the upper limit of normal. Fifty-six per cent of patients had raised urinary magnesium levels. Urinary phosphate, creatinine, urate and sodium were normal prior to bran treatment.

Sixty-two of the 72 patients (86%) developed a statistically significant reduction in urinary calcium excretion during treatment with unprocessed bran (Table 2). In 28 patients the urinary calcium levels returned to within the normal range during treatment. They had had lower mean pre-trial urinary calcium levels. The remaining 34 patients with higher mean pre-trial urinary calcium levels lowered their urinary calcium excretion significantly but not to within the normal range.

There were no changes in serum calcium, phosphate, alkaline phosphatase, urate or magnesium during treatment. There was no significant change in urinary magnesium, sodium or phosphate excretion during treatment with bran; in the responding patients, however, a non-significant rise in urinary phosphate and magnesium excretion was present in the 10 patients with no reduction in urinary calcium excretion.

Discussion

A reduction in the incidence of stone recurrence is the aim of treatment of patients with idiopathic hypercalciuria. Most patients find long-term dietary or therapeutic regimes difficult to adhere to and may lapse from treatment if not carefully supervised (Baker and Mallinson, 1979; Backman *et al.*, 1980). Since only approximately 50% of patients will develop recurrent stones, lifelong therapy with its associated problems may be difficult to justify, particularly for those patients who will not develop recurrent stones even if they cannot be predicted.

All patients should be advised to increase their daily fluid intake and to restrict their dietary calcium intake to less than 700 mg daily if possible.

Sodium cellulose phosphate binds calcium in the intestine and prevents calcium absorption. It has been shown by Blacklock and Macleod (1974) that a significant reduction in stone formation can be achieved in these patients with cellulose phosphate. However, Backman *et al.* (1980) found in a long-term study of treatment with sodium cellulose phosphate that despite significant reduction in urinary calcium excretion there was no improvement in recurrent calcium oxalate stone formation over a period of 2 years. They also reported side effects such as gastrointestinal discomfort, which necessitated withdrawal of treatment. Rose and Harrison (1974) also described an incidence of diarrhoea of 25%. Backman *et al.* (1980) suggested that sodium cellulose phosphate was more applicable to the treatment of patients with calcium phosphate stones.

Thiazide diuretics, which probably act by altering renal handling of calcium, are more effective in the treatment of patients with renal hypercalciuria. However, Rose and Harrison (1974) described a successful reduction in urinary calcium excretion in only 54% of patients treated with bendrofluazide.

From the results of this study it is shown that treatment with unprocessed bran produced an effective reduction in urinary calcium excretion in 86% of patients. Urinary magnesium, phosphate and sodium remained unchanged during the study.

The successful effect of bran on calcium excretion is probably related to several factors. The major effect is due to the combination of phytic acid with dietary calcium in the intestine to form calcium phytate which is then excreted. Phytate may also bind calcium as a complex, thus preventing its absorption (Macleod and Blacklock, 1979). Macleod and Blacklock (1979) have shown that wheat bran inhibits glucose absorption which through its contact with the intestinal mucosa normally enhances calcium absorption. We suggest also that a reduction in intestinal transit time occurs during bran therapy, which reduces the time available for calcium absorption to occur. Of the 72 patients studied, 10 did not respond to bran therapy. Each patient admitted to having completed the course of treatment as directed. The failure to respond is difficult to explain, particularly the insignificant increase in urinary magnesium and phosphate excretion. It is possible, however, that a proportion of the non-responding patients could belong to the group of renal hypercalciurics.

The majority of patients experienced a change in bowel habit with a more frequent, looser motion during treatment. Many patients felt generally better during the study. Some patients found the fine unprocessed bran particularly unpalatable. However, proprietary forms of bran which would be used in long-term treatment are easier to ingest because particle size is larger.

It is hoped that unprocessed bran will maintain a reduction in urinary calcium excretion over a long period and a subsequent fall in the incidence of recurrent stone formation will occur. Twenty-five patients with idiopathic hypercalciuria have completed up to 6 months' continuous therapy with unprocessed bran and no stone recurrences have been reported.

Acknowledgement

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Urotheliai Carcinoma of the Kidney and Ureter

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Summary—Two hundred and three patients with upper tract urothelial tumours were reviewed. Eighty had pelvicaliceal tumours, 90 ureteric tumours, and 33 multifocal tumours of both pelvis and ureter. Two hundred patients had transitional cell carcinomas and 3 had squamous cell carcinomas.

The overall corrected 5-year and 10-year survival rates were 59.7% and 41.1% respectively.

Widespread multifocal occurrence, poor differentiation, penetration of the muscle coat and conservative resection of tumours predisposed to a poorer prognosis.

During the 25 years 1955 to 1979, 203 patients with upper tract urothelial tumours were treated in the St Peter's Hospitals. The clinical features, aetiological factors, treatment, human pathology and prognosis are presented.

Patients

There were 156 males and 47 females (ratio M : F = 3.3 : 1) and their ages ranged from 29 to 88 years, average 62.1. They fell into 3 groups:

Group I Tumours of the Pelvicaliceal System (TCCK)

Eighty patients—81 tumours.

Group II Tumours of the Ureter (TCCU)

Ninety patients—91 tumours.

Group III Tumours of Both the Pelvis and Ureter (TCCK + U)

Thirty-three patients—33 tumours.

One hundred and forty-eight presented with primary upper tract carcinomas; the remaining 55 had had previous urothelial carcinomas of the bladder (45), kidney (8), or both (2).

In 200 patients the tumours were transitional cell (TCC), 2 having bilateral pelvicaliceal and ureteric tumours respectively. Three further patients had squamous cell carcinomas (Sq CC). The tumours were graded as well differentiated, of intermediate grade, or poorly differentiated, and staged according to the UICC (1978) classification.

Presentation (Table 1)

The commonest presenting symptom was haematuria; this occurred in 129 patients, being associated with loin pain in 32. Twelve presented with loin pain alone.

Of the 55 patients already under follow-up for TCC 24 returned with new symptoms, while in 31 upper tract tumours were discovered during routine follow-up.

The tumours of 5 patients were found during surgery for benign conditions and one was detected by industrial urine cytology screening. The presentation is unknown in a final case.

Nineteen patients had palpable kidneys.

Table 1 Presentation of 203 Patients with Upper Tract Urothelial Carcinoma

Haematuria (129):	
painless	97
loin pain	32
Loin pain alone	12
Follow-up for TCCB (47):	
new symptoms	19
no symptoms	28
Follow-up for TCCK (8):	
new symptoms	5
no symptoms	3
Others	7
Total	203

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Investigative Diagnosis of 205 Upper Tract Urothelial Carcinomas in 203 Patients

Investigation	*Groups*			
	Total	*I—TCCK*	*II—TCCU*	*III—TCCK + U*
IVU alone	45	32	8	5
IVU + cytology	19	13	4	2
IVU + cystoscopy	18	2	14	2
NFK + cystoscopy	17	—	7	10
Cystoscopy alone	19	—	19	—
Initial Investigation	118 (58%)	47 (58%)	52 (64%)	19 (58%)
RUP alone	42	15	19	8
RUP + cytology	6	3	3	—
RUP + cystoscopy	3	3	—	—
Antegrade pyelogram	8	—	5	3
Exploration	25	13	9	3
Chance finding	3	—	3	—
Subsequent investigation	87	34	39	14

IVU = intravenous urogram.
NFK = non-functioning kidney.
RUP = retrograde ureteropyelogram.

Investigation (Table 2)

Initial investigation by intravenous urography, urine cytology and cystoscopy established the diagnosis in 118 patients (58%). The urographic appearances were frequently inconclusive, but positive cytology or tumour or blood seen emanating from the ureteric orifice at cystoscopy often confirmed a suspected diagnosis.

In 85 patients, of whom 2 had bilateral tumours, making 87 in all, retrograde or antegrade pyelography was necessary, but even then 24 patients came to exploratory surgery without a definite diagnosis of tumour having been made.

In 3 patients who had a cystectomy for TCCB, separate tumours were found in the ureteric stumps on pathological examination.

Aetiological Factors

Incidence

During the 25 years 1955 to 1979 the average incidence of new upper tract tumours was 8.1 cases/annum compared with approximately 190 cases/annum of new bladder tumours. For no apparent reason there was a sudden rise to 15.8 cases/annum over the brief period 1967 to 1971. A similar rise was reported in Bristol at this time (Williams and Mitchell, 1973).

Occupation

Three patients gave a history of prolonged contact with carcinogens: 2 were rubber manufacturers, one being a "compounder", and one worked with photographic chemicals. Possible contact occurred in 6 more patients: 2 newspaper printers, 2 hairdressers, one gas worker, and one oil merchant. Two further patients were garage mechanics. The rubber compounder and the 2 printers had intermediate grade TCCs; the rest were well differentiated.

Smoking

Seventy-five patients were smokers, 46 were non-smokers, and in 82 cases smoking habits were not recorded. However, since 1970 better case records have confirmed a greater tendency for urothelial tumours to develop in smokers, as there were 44 smokers, 25 non-smokers, and no record obtainable from 9 patients. Tumour differentiation differed little from the overall pattern.

Drugs

Of 5 patients who had taken long-term analgesics, one had a TCCK, 3 had TCCUs, while the only known analgesic abuser had a poorly differentiated multifocal TCCK + U which had invaded the renal parenchyma.

Infection, Stones and Congenital Abnormalities

At first presentation 31 patients had urinary tract infections. In Group I both cases of Sq CC were related to chronic calculus disease, one having a

Table 3 Relationship of Upper Tract Tumours to Carcinoma of the Bladder

TCCB	*Total*	*Groups*		
		I—TCCK *80 patients*	*II—TCCU* *90 patients*	*III—TCCK + U* *33 patients*
Preceding	48	6	35	7
Concurrent	39	8	17	14
Subsequent	27	11	10	6
Total	114	25 (31.3%)	62 (68.9%)	27 (18.8%)

cystine staghorn stone and the other associated with leukoplakia and pelviureteric junction obstruction. Three patients within this group with TCCs also had pelviureteric junction obstruction, one had a medullary sponge kidney and one had a tumour in the obstructed moiety of a duplex kidney. Four patients had no apparent predisposing factors.

There were 20 infected patients in Groups II (18) and III (2). The SqCC was associated with obstruction, *Proteus* infection, and leukoplakia secondary to achalasia of the lower ureter. Three patients with stump carcinomas had infections. Three patients had mixed organism infections, one associated with bladder calculi and the other 2 with ileal conduit urinary diversions. Altogether 14 of these 20 cases were associated with ureteric obstruction by the tumour.

Stump Carcinoma—8 Cases

This term denotes a carcinoma arising in the ureteric stump following a previous nephrectomy for a urothelial tumour (7 cases) or a benign condition (1 case). Five tumours were well differentiated, 2 of intermediate grade, one poorly differentiated and 5 were multifocal in origin. In the 7 cases of previous urothelial malignancy the time interval ranged from 20 months to 5 years, average 39 months, whereas in the patient whose kidney had been removed for a calculus pyonephrosis, the interval was 37 years. Six of these 8 patients survived more than 5 years.

Relationship to Transitional Cell Carcinoma of the Bladder (Table 3)

Forty-eight patients had had TCCB present from 2 months to 20 years (average 7 years) before discovery of an upper tract tumour. Thirty-nine more had concurrent TCCB discovered at presentation and 27 more developed TCCB 3 months to 7½ years (average 18 months) after excision of their upper tract tumours. Therefore 114 patients (56%) had TCCB before, with, or after an upper tract tumour. As is shown in Table 3, TCCB is much commoner in association with ureteric tumours.

In Groups II and III 10 of the 42 cases of preceding TCCB and 28 of the 31 concurrent cases involved the ureteric orifice, whereas no cases in Group I involved the orifices. The term "involved" is purely clinical and describes what the endoscopist saw, often without distinction between tumours encroaching upon rather than protruding from the orifice.

Following excision of the upper tract tumours the recurrence rates for TCCB in the 3 groups became very similar.

In 73 cases in which the histology of the TCCB was known the differentiation was the same as in the upper tract tumour in 63 (86.3%), suggesting that tumour differentiation remains largely consistent both temporally and spatially.

Treatment (Table 4)

Seventy-six patients underwent nephroureterectomy plus excision of the intramural ureter with a surrounding cuff of bladder. A further 7 underwent the procedure in 2 stages, when the full extent of the tumour was recognised. Another 29 had a nephroureterectomy with ligation of the ureter flush with the bladder.

Fifteen patients underwent nephrectomy, leaving all of the lower ureter, and a further 21 had palliative, simple nephrectomies for advanced tumours.

Eleven had elective local resections for solitary pelvicaliceal (7) or ureteric tumours (4) and in 30 the lower ureter was resected, usually followed by vesical reimplantation.

Table 4 Treatment of 203 Patients with 205 Upper Tract Urothelial Carcinomas

Nephroureterectomy + cuff of bladder	76
Nephroureterectomy without cuff of bladder	29
Nephroureterectomy in 2 stages	7
Nephrectomy + upper ureterectomy	15
Palliative simple nephrectomy	21
Local resection (11):	
renal	7
ureteric	4
Resection of lower ureter	30
Excision of stump carcinoma	8
Others	8
Total tumours	205

Table 5 The Histological Differentiation of 205 Upper Tract Urothelial Carcinomas

Differentiation		*Total*	*Groups*		
			I—TCCK	*II—TCCU*	*III—TCCK + U*
TCC	Well	131	57	57	17
	Intermediate	45	17	20	8
	Poor	26	5	13	8
Squamous cell		3	2	1	—
Total		205	81	91	33

The 8 patients with "stump carcinomas" had the residual stump excised. Cystectomy and excision of the lower ureters was performed in 5 patients with concurrent TCCB and one underwent a palliative unilateral ureterosigmoidostomy for inoperable TCCB plus bilateral TCCUs. One tumour of the intramural ureter was resected transurethrally.

Tumour Pathology

Side and Site

There were 205 tumours in 203 patients, 108 being right-sided, 95 left-sided, and one at the Y anastomosis with an ileal conduit. The side of one ureteric tumour is unknown.

Differentiation (Table 5)

Of the 205 tumours 131 (63.9%) were well differentiated TCCs, 45 (22%) were of intermediate grade, and 26 (12.7%) poorly differentiated TCCs. Three patients (1.5%) had squamous carcinomas.

Stage (Table 6)

The 205 tumours included 87 (42.4%) which were non-invasive (pa), 18 (8.8%) which had breached the basement membrane to invade the stomal cores of papillae (pla), and 29 (14.1%) which had reached the lamina propria (plb). Superficial invasion of the muscle coat (p2) was uncommon, being found in 14 cases (6.8%) compared with deep invasion in 28 (13.7%) (p3) or actual penetration in 25 (12.2%) (p4) cases. Four of the pelvicaliceal tumours were growing up the lumina of the collecting ducts without penetrating the basement membrane and were substaged p4a to distinguish them from tumours invading the renal parenchyma (p4b).

None of the ureteric tumours had invaded adjacent organs or the posterior abdominal wall (p4).

Prognosis (Table 7)

The overall 5-year survival rate (YSR) was based on 144 of the 172 patients operated on before 1975 after excluding 17 who died of unrelated causes and 11 lost to follow-up within 5 years of surgery. Eighty-six (59.7%) survived more than 5 years.

Similarly, the 10-YSR was based on 90 of the 125 patients operated on before 1970 after excluding 24 patients dying of unrelated causes and 11 lost to follow-up. Thirty-seven (41.1%) survived more than 10 years.

Survival rates for Groups I and II were very similar, being 64.3% and 67.2% respectively at 5 years and 47% and 45.9% at 10 years. The rates were much worse for the multifocal tumours of Groups III, being 33.3% and 21% at 5 and 10 years respectively.

Table 6 The Histological Staging of 205 Upper Tract Urothelial Carcinomas

Group	*Total*	*Tumour stage*						
		pa	*pla*	*plb*	*p2*	*p3*	*p4a*	*p4b*
I—TCCK	81	37	8	10	—	6	3	17
II—TCCU	91	40	7	13	11	20	—	—
III—TCCK + U	33	10	3	6	3	2	1	8
Total	205	87	18	29	14	28	4	25

Table 7 Overall Corrected Survival Rates in Patients with Upper Tract Urothelial Carcinomas

Survival Rates	*Groups*							
	I—TCCK		*II—TCCU*		*III—TCCK + U*		*All patients*	
	T	S	T	S	T	S	T	S
5-Year (pre-1975)	56	36 (64.3%)	61	41 (67.2%)	27	9 (33.3%)	144	86 (59.7%)
10-Year (pre-1970)	34	16 (47%)	37	17 (45.9%)	19	4 (21%)	90	37 (41.1%)

T = total number of patients; S = survivors.

Discussion

Relationship of Differentiation to Prognosis

The overall corrected 5-YSR was 73.1% (68/93 patients) for well differentiated tumours, 40% (12/30) for those of intermediate grade and 33.3% (7/21) for poorly differentiated ones. Therefore the poorer the differentiation the worse the prognosis. However, in Group III patients the 5-YSR for well differentiated tumours was much poorer than in the other 2 groups, being only 50% (7/14 patients) compared with 73.7% (28/38) for Group I and 80.5% (33/41) for Group II. This suggests that even if tumours are well differentiated their multiplicity predisposes to early metastasis.

Relationship of Stage to Prognosis

The overall corrected 5-YSR for patients with tumours not penetrating beyond the midpoint of the muscle coat of the ureter and pelvis (pa-p2) was 72.5% (74/102 patients), while for the 42 patients with tumours invading deeply into or beyond the muscle (p3-p4) it was 31% (13/42 patients). Though only thin, the integrity of the muscle coat appears to be of considerable prognostic importance.

Of 4 patients whose tumours were growing up the collecting ducts of the kidney (p4a), one was lost to follow-up, one died of TCC, and 2 survived more than 5 years, suggesting a better prognosis for these patients than for those with renal parenchymal invasion.

Relationship of Bladder Cancer to Prognosis (Table 8)

Before 1975 11 Group I, 45 Group II and 18 Group III patients had had a prior or concurrent TCCB. If these patients are excluded from the corrected 5-YSR calculations, Table 8 shows that only in Group II was there an appreciable improvement in survival rate compared with the overall ratios for the groups. Therefore the prior or concurrent involvement of the bladder does not significantly worsen prognosis, except in patients with ureteric tumours.

Relationship of Latent Period to Prognosis

We refer to the "latent period" as the time from the onset of symptoms to the excision of all upper tract tumour. This was known in 134 of the patients with no prior TCCB and ranged from 2 to 208 weeks. The average latent periods for the groups were: Group I—25 weeks, Group II—32 weeks, and Group III—60 weeks. It appeared in Groups II and III that the presence of a TCCB diverted attention from a latent upper tract tumour and on 6 occasions in Group III a lower ureteric

Table 8 Relationship of Prior or Concurrent Bladder Cancer to Prognosis (1955 to 1974, with Exclusion of Patients Lost to Follow-up or Dying of Unrelated Causes Within 5 Years of Surgery)

Group	*All patients*		*+TCCB*		*No TCCB*	
	No.	*5-YSR*	*No.*	*5-YSR*	*No.*	*5-YSR*
I—TCCK	56	36 (64.3%)	8	5 (62.5%)	48	17 (64.6%)
II—TCCU	61	41 (67.2%)	37	15 (40 5%)	24	19 (79.2%)
III—TCCK + U	27	9 (33.3%)	16	5 (31.3%)	11	4 (36.4%)
Total	144	86 (59.7%)	61	25 (41%)	83	40 (48.2%)

5-YSR = 4-Year Survival Rate.

tumour was excised, leaving behind an unnoticed pelvicaliceal one. Fortunately, a long latent period does not seem to worsen the prognosis since the corrected 5-YSR of 61.5% for patients with a latent period longer than 6 months is little different from the overall 5-YSR of 59.7%.

Conservative Versus Radical Surgery in Relation to Prognosis

In Group I and II patients with discrete tumours, 42 underwent radical nephroureterectomy compared with 37 who had an elective local resection. The corrected 5-year survival figures for the 2 groups were 34/38 (89.5%) and 16/27 (59.3%) respectively. Furthermore, if patients who had had a preceding TCCB are excluded, the radical versus conservative figures are respectively 28/30 (93.3%) and 9/16 (56.3%). These figures do not support the argument for more conservative surgery.

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The Treatment of Ureteric Stones
Report on 1120 Patients

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Summary—A consecutive series of 1120 patients with ureteric stones is presented. Conservative and surgical treatment is discussed and the results of ureteric catheterisation, dilatation, transurethral manipulation and extraction, ureteric meatotomy and ureterolithotomy are presented.

More than 80% of ureteric stones are passed spontaneously, but the behaviour of any particular stone cannot be predicted; large stones may pass spontaneously and unexpectedly, while small ones, expected to pass spontaneously, may be held up in the ureter. Impaction of a stone in the ureter causes congestion, oedema and inflammatory change; these result in the formation of "bars", *i.e.* oedematous areas of the ureteric mucosa projecting into the lumen, and the oedema may be so marked as to engulf the stone. Considerable thickening of the ureter occurs at the site of impaction; the upper ureter dilates and, in unrelieved cases, dilatation, thinning and fibrotic changes in the wall of the ureter may result.

Most stones are passed within 6 weeks and the smaller and lower down the ureter the stone is, the more likely it is to pass. The likelihood of an individual stone being passed spontaneously has been studied by Sandegard (1956); his views are paraphrased as follows:

(1) Small stones (X-ray width less than 4 mm) in the lower half of the ureter will usually pass spontaneously (93% within 6 weeks of the onset of symptoms).
(2) Small stones in the upper half will usually be passed spontaneously (81%). Small stones in the upper ureter cause more obstruction than in the lower half of the ureter.
(3) Medium-sized stones (4-6 mm) in both the upper and lower half of the ureter are often passed spontaneously (50%). However, medium stones in the upper half of the ureter are associated with a high incidence of renal complications due to obstruction.
(4) Large stones (greater than 6 mm) in either the upper or lower ureter rarely pass spontaneously and involve a considerable risk of serious complications.

There is no urgent reason for removing a ureteric stone unless (1) the pain is severe, (2) there is persisting or increasing dilatation, (3) the patient becomes pyrexial, or (4) there is evidence of pyelonephritis or pyonephrosis. The size and position of the stone may also indicate that early intervention is necessary.

The aim of this study was to evaluate the various forms of surgical treatment for ureteric stone.

Patients and Methods

A consecutive series of 1120 patients with ureteric stones seen over a period of 10 years at the Urological Department of the Meath Hospital is presented. The figures include cases previously reported by Butler and O'Flynn (1973). They do not represent all patients with ureteric stones seen during that period but only those who were admitted to hospital. Of a total of 1120 patients surgical treatment was necessary in 735.

From the department records urinary stones accounted for about 4% of all patients admitted

Table 1 Ureteric Stones—Results of Ureteric Catheterisation

Total procedures	173	
Stones passed spontaneously after catheterisation	65	(37.5%)
Ureterolithotomy following ureteric catheterisation	82	(47.3%)
Lost to follow-up with stones still in ureter following catheterisation	13	(7.5%)
Unsuccessful catheterisation	13	(7.5%)

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Ureteric Stones—Results of Ureteric Dilatation

Total procedures	19	
Stones passed spontaneously after dilatation	4	(21.0%)
Ureterolithotomy following dilatation	13	(68.4%)
Lost to follow-up with stones still present after dilatation	2	(10.5%)

for operation. Of a series of 1639 stone patients admitted over a 10-year period ureteric stones constituted approximately 30%.

The types of surgical treatment in this series were as follows: ureteric catheterisation, ureteric dilatation, transurethral manipulation and extraction, transurethral meatotomy and ureterolithotomy. Ureterostomy was very occasionally done as a palliative procedure or as an adjunct to ureterolithotomy. Nephrectomy was rarely necessary.

Surgical treatment was carried out by 3 urologists and successive registrars and senior registrars who were working in the department over the period.

Ureteric Catheterisation (173 procedures)

This was usually done (1) as a simple diagnostic measure to determine whether a specific opacity was a ureteric stone, (2) where only one catheter could be passed prior to a projected stone manipulation, or (3) when a small stone, considered likely to pass, was lodged high up in the ureter. Usually the catheter was immediately withdrawn and the results of this procedure are shown in Table 1.

Ureteric Dilatation (19 procedures)

Dilatation or double catheterisation of the ureter was done with 2 No. 5 FG ureteric catheters when the stone was impacted too high up in the ureter for basket removal, or as a preliminary to attempting and failing to pass a stone basket. Occasionally the catheters were twisted on each other in the hope that they might twist within the ureter and entrap the stone. This manoeuvre was never successful. Usually the catheters were withdrawn but, in a few instances, they were left *in situ* for up to 48 h. The results of double catheterisation, in effect dilatation of the ureter, are shown in Table 2.

Table 3 Ureteric Stones—Results of Transurethral Manipulation with Stone Basket

Total procedures	173	
Stones extracted	52	(29.8%)
Stones passed spontaneously after manipulation	67	(38.5%)
Ureterolithotomy following transurethral manipulation	18	(10.3%)
Lost to follow-up with stones still present after transurethral manipulation	5	(2.8%)
Meatotomy + transurethral manipulation	23	(13.2%)
Unsuccessful transurethral manipulation	8	(4.5%)

Transurethral Manipulation and Transurethral Extraction (173 procedures)

The use of stone baskets for the removal of stones can be a very satisfactory procedure and in some series a high rate of recovery has been reported. In this series the Councill extractor was used mostly in the early part of the series. The technique was to pass 2 catheters up the ureter initially, remove them, and then pass the stone basket. Manipulation may be defined as the successful passage of the extractor above the stone but the failure to engage and extract it. Spontaneous passage is frequent after manipulation (Table 3).

Transurethral Ureteric Meatotomy (27 procedures)

The indication for this procedure was X-ray evidence of a stone in the intramural part of the ureter and the cystoscopic finding of an area of oedema above and around the ipsilateral ureteric orifice. Vertical incision of the ureteric orifice with an endoscopic knife electrode or Collings knife or knife urethrotome usually revealed the stone which could then be levered into the bladder and removed transurethrally. Table 4 shows the results of this procedure.

Ureterolithotomy (312 procedures)

In this series in 3 instances the stone could not be located at the expected site. In 2 cases the stone had moved into the intramural ureter and was removed after ureteric meatotomy, one transurethral, one transvesical. In one case the stone was not located but was passed spontaneously within a week after operation. Temporary ureterostomy was occasionally done prior to ureterolithotomy where, for some reason, immediate operation was not possible and sometimes as an adjunct to ureterolithotomy to ensure good renal drainage (Table 4).

Discussion

The pathophysiology of acute ureteric obstruction

Table 4 Ureteric Stones—Results of Surgical Treatment

Procedure	*No. of procedures*	*Stone removed*	*Stone passed*	*Successful (%)*
Catheterisation of ureter	173		65	37.5
Dilatation of ureter	19		4	21.0
Transureteric meatotomy	27	26		96.2
Transurethral manipulation	173	52	67	68.3
Ureterolithotomy	312	309		99.0
Nephrectomy	5	5		100.0
Ureterostomy	26			

has been well described by Rose and Gillenwater (1973). Initially there is a rise in intraluminal pressure, associated with increasing frequency and amplitude of ureteric contractions and a rapid rise in intraureteric pressure above the site of obstruction. This phase may last up to 3 h and be succeeded by a period of high pressure with ureteric contractions; this is followed by a fall in intraureteric pressure and cessation of all contractions. The kidney apparently continues to secrete urine which must now be transported in the incompetent ureter by hydrostatic forces only.

Total obstruction by a stone is a rare occurrence. It appears that urine usually leaks past the stone and the kidney resumes function, but the ureter may remain dilated and continue to dilate as long as the obstruction is present. It is evident from this study and from clinical experience that no form of drug therapy presently used is likely to affect the passage of a stone. Even a high fluid intake is probably useless, since the affected kidney may have diminished or absent function and the excess fluid may be excreted by the opposite kidney.

What exactly is achieved by single or double catheterisation is speculative, but it seems likely that the passage of the catheters between the stone and the ureteric mucosa alters the relationship of the oedematous mucosa to the stone or possibly moves the stone itself.

Much the same can be said of transurethral manipulation with a stone basket, but in this case the chances of moving the stone must be greater. Given the indications outlined here, the figures clearly indicate that these procedures are worth doing. Similarly, the results of transurethral ureteric meatotomy are satisfactory.

The successful removal of stones with the basket seems, in this series, to be considerably less frequent than in some other reported series. No explanation can be offered for this. The main indication in this group has been the presence of a stone in the lower third of the ureter and the allowance of a reasonable period of time for its spontaneous passage. It is possible that some of the stones were larger than those operated on elsewhere and some were manipulated with the basket because it was felt that a stone that reached the lower third of the ureter would be suitable for extraction even though it appeared larger than one would like. Whatever the failure rate, the incidence of spontaneous passage after manipulation is high.

Ureterolithotomy is a highly successful procedure and failure to recover the stone by this method is rare.

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Transurethral Ureterolithotomy

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Summary—The technique of transurethral ureterolithotomy for calculi impacted in the intramural ureter is described. Follow-up date on a group of 30 patients treated by this method are presented.

Vesicoureteric reflux was found to occur in almost 50% of cases. The presence of reflux was not found to cause symptoms, infection or renal destruction. Therefore transurethral ureterolithotomy is recommended for the removal of intramural ureteric stones not suitable for basket extraction.

Surgical removal of a stone impacted in the intramural ureter is technically difficult. The therapeutic philosophy of urologists varies enormously in the approach to the obstructive ureteric calculus. In our own practice we have found that 51% of ureteric stones that warranted removal were lodged in the intramural ureter. Of these, 7% were dealt with by open operation, 34% were extracted endoscopically with a stone basket, and 10% were removed transurethrally using a Collings knife mounted on a resectoscope. The technical aspects of open operation (Maynard and Landsteiner, 1972; Barnhouse *et al.*, 1973) for stone in the intramural ureter as well as endoscopic extraction (Constantian, 1974; Walsh, 1974) and transvaginal removal (O'Boyle and Gibbon, 1976; Farkas and Firstater, 1979) have been well described in the past. The purpose of this study was to describe the technique of transurethral ureterolithotomy and present the results of the operation in a group of 30 patients with long-term follow-up.

Patients and Methods

Over the past 8 years transurethral ureterolithotomy was performed on 48 cases in our unit. Of these, 30 were available for follow-up. Of the 30, 25 were male and 5 were female. The average age was 40 years.

On X-ray any stone located at or below the ischial spine was considered to be within the intramural ureter. It may frequently appear to lie above the bladder on the plain or post-micturition films (Fig. 1).

The 24 FG resectoscope with a Collings knife was used to open the ureter in the intramural position.

In 5 of the 30 cases studied the stone was visible

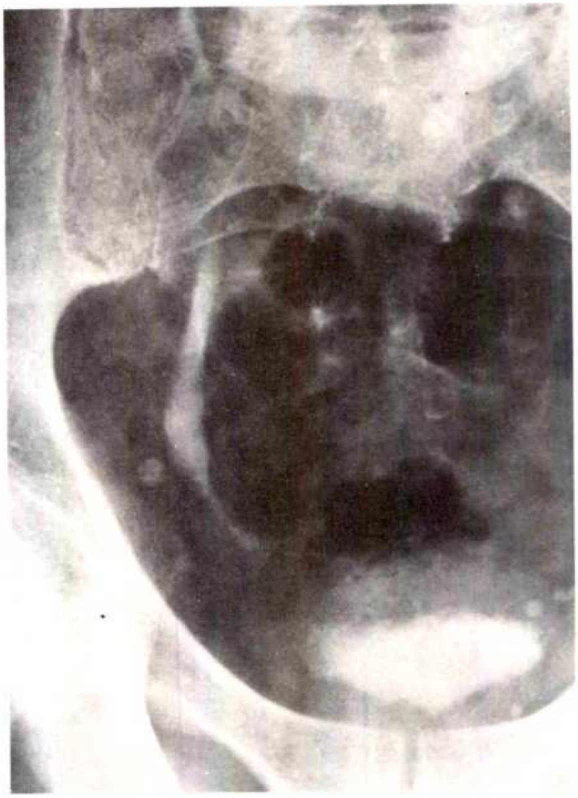

Fig. 1 Radiographic location of stone in intramural ureter. The stone appears above the empty bladder but was removed by transurethral ureterolithotomy.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

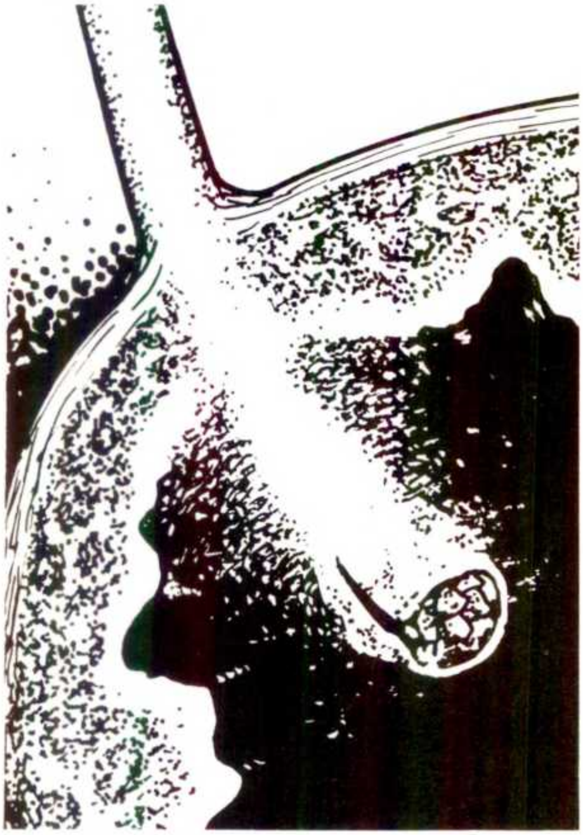

Fig. 2 Incision of lateral edge of ureteric meatus.

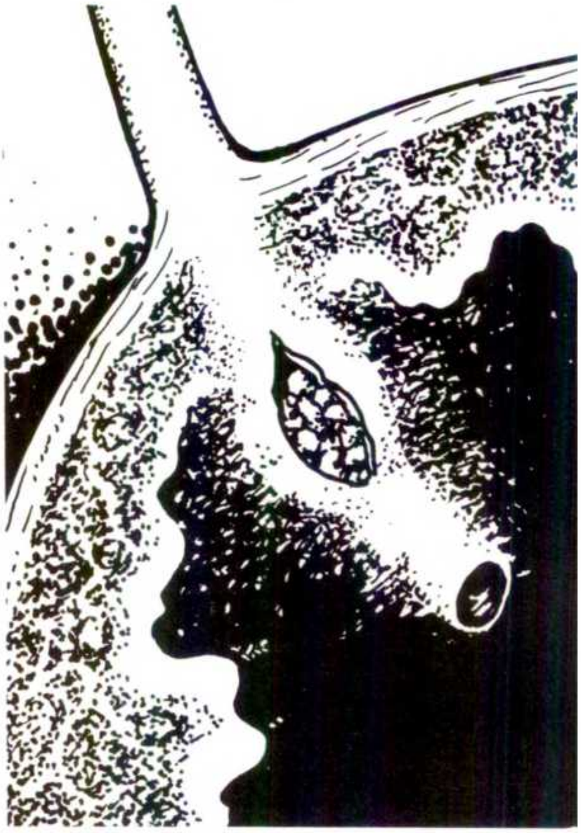

Fig. 3 Incision in anterior ureteric wall over underlying stone.

at the ureteric orifice (Fig. 2). In these cases a meatotomy was performed of sufficient length to facilitate removal of the stone. The ureteric orifice was incised on the lateral aspect. In general, the length of this incision was no more than a few millimetres.

In the majority of cases the stone was seen to bulge the intramural ureter above the meatus (Fig. 3). In such instances an incision was made in the anterior wall of the ureter with preservation of the meatus. Despite the surrounding oedema the ureteric orifice was usually clearly visualised. This approach was used in 20 of the 30 cases studied.

In 5 cases the stone was located at the point of entry of the ureter into the bladder (Fig. 4). In these cases no bulge was visualised. However, the stone could be seen to move under the bladder mucosa when an attempt was made to get a stone basket past it. When the basket could not be advanced beyond the stone, a diathermy electrode was advanced to the point of the obstructing stone, the exact location of the obstruction was identified as seen by movement of the bladder mucosa and that point on the mucosa was then marked with diathermy. The intramural ureter could then be accurately incised over the stone and the stone delivered into the bladder. In most of these procedures, when the stone was free in the bladder it could be extracted by engaging it in the resectoscope sheath and removing it with the instrument. In some cases, however, resort to an Ellick evacuator was necessary.

Results

The results of follow-up of these cases are summarised in Figure 5. The length of follow-up varied from 1 to 8 years, with an average follow-up period of 4 years. In all instances the patients were followed up by clinical examination, urine analysis and culture, intravenous urogram and micturating cystogram. Of the 30 cases studied, 3 complained of loin pain for about 3 months after the operation. This pain was associated with urination and considered to result from vesico-

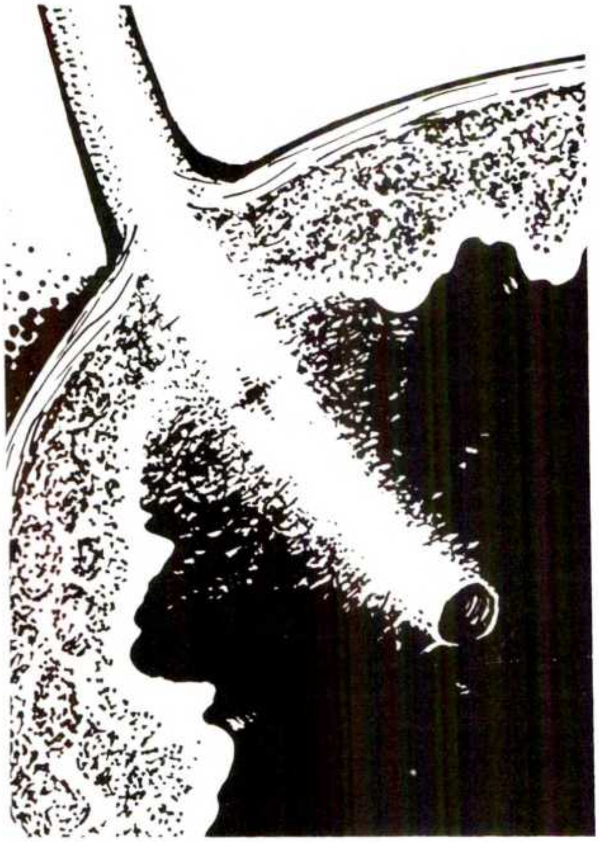

Fig. 4 Diathermy electrode mark depicting exact location of underlying intramural stone.

ureteric reflux. Urine cultures were positive in 3 other patients who complained of slight dysuria. This occurred only during the early post-operative period and disappeared later. On intravenous urography 4 patients had developed ipsilateral recurrent stones. In no case was there radiographic evidence of pyelonephritic scarring.

On micturating cystography vesicoureteric reflux was found to occur in 14 of the 30 cases. In 9 cases it was considered grade 1, with regurgitation into the pelvic ureter without any evidence of ureteric dilatation. In a further 5 cases regarded as grade 2, contrast medium filled the renal pelvis and collecting system but again there was no evidence of dilatation.

The average post-operative hospital stay for patients in this study was 4 days. There was no mortality or significant post-operative morbidity.

Discussion

Operation for stone in the intramural ureter is a common procedure in any urological unit. Because of the prevalence of stone disease in middle-aged men, who are frequently obese with a narrow pelvis, the technical difficulties of this procedure are widely appreciated as well as the inherent risk of thrombo-embolism following pelvic surgery. It is axiomatic that since the introduction of the cystoscope, urologists should attempt removal of such calculi via the transurethral route. This has been the concern of urologists since Young prised a stone cystoscopically from the ureteric orifice in 1902 (Constantian, 1974). In 1926 Bumpus described transurethral meatotomy for stones impacted at the ureteric orifice. This procedure has been widely used since then, but the concept of incising the intramural ureter as described here was first suggested by Walsh (1974).

Despite the attraction of the transurethral route, the significance and frailty of the ureterovesical antireflux mechanism, as described by Hutch in 1962, dampened the enthusiasm for transurethral incision in this area. Whereas reports in the literature by Roper and Smith (1965) and McAdam and James (1967) have advocated transurethral meatotomy as a safe procedure, the rapid destruction of renal tissue by reflux in the adult, as suggested by McGovern and Marshall in 1968, created doubts. Consequently open operation using the transvesical route (Maynard and Landsteiner, 1972; Barnhouse *et al.*, 1973) became fashionable in cases where basket extraction was not feasible.

We conclude that transurethral ureterolithotomy is a safe procedure. While reflux will be found in almost 50% of these cases on cysto-

Total number of cases:	30 (25 male, 5 female)
Age:	20-66 years (average 40 years)
Follow-up:	1-8 years (average 4 years)
Pain:	4 (of short duration)
Urine culture:	2 positive during early post-op. period
IVU:	Recurrent stone—4 cases Pyelonephritic changes—Nil
Micturating cystogram:	Reflux: Grade 1—9 Grade 2—5 Grade 3—0
Average post-op. hospital stay:	4 days

Fig. 5 Results of follow-up of 30 patients following transurethral ureterolithotomy.

graphy, our findings support those of Lalli and Lapides (1968) as well as Lipsky and Chisholm (1971), and Moore (1979) that such reflux is not associated with infection, dilatation or progressive renal damage. The procedure is advocated particularly for stones that are not amenable to removal by basket extraction. The absence of long-term ill effects on kidney function, together with the fact that the average post-operative stay was only 4 days, are obvious advantages over open operations.

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Retroperitoneal Fibrosis
Practical Problems in Management

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Summary—Nineteen patients with retroperitoneal fibrosis were reviewed. Eighteen patients had idiopathic disease and one had taken methysergide for 15 years. Primary bilateral ureterolysis was undertaken in 13 cases. Five patients developed problems due to extension of their disease after surgery. Low dose steroids may be useful in the treatment of patients with raised sedimentation rates after surgery in order to prevent late manifestations of the disease.

In spite of its rarity, idiopathic retroperitoneal fibrosis is of great urological importance because it produces bilateral ureteric obstruction and renal failure.

Patients and Methods

Between 1967 and 1980, 19 patients presented with retroperitoneal fibrosis. One of these had taken methysergide for 15 years but the remaining cases were idiopathic. Arterial and malignant causes of retroperitoneal fibrosis have been excluded from these figures. Eleven of the patients were males and 8 females. Their ages ranged evenly between 39 and 73 years. No patient presented with an Erythrocyte Sedimentation Rate (ESR) of less than 45 mm in the first hour (Westergren), and the highest ESR recorded was 147 mm; 11 of the patients had an ESR on presentation in excess of 90 mm. No other laboratory investigation, including full auto-immune profiles, was of any diagnostic value.

Thirteen patients underwent primary bilateral ureterolysis; 2 had had ureteric surgery carried out before referral and 4 were managed conservatively. Ureterolysis was carried out under the same anaesthetic as confirmatory ureterography. The ureters were freed from the renal pelvis to the back of the bladder no matter how short a length was involved in the fibrosis. After lysis the ureters were safeguarded by retroperitoneal lateralisation or intraperitoneal translocation. In 2 cases omental wrapping was used since neither of the first 2 methods was appropriate. In 11 kidneys proximal drainage was employed until ureteric function had been shown to have recovered by descending ureterography: nephrostomy was ordinarily used but early in the series one patient had bilateral pyelostomies made.

Results

Two of the 13 patients have died, one at 2.2 years from progressive renal failure, and the other at 1.5 years from cardiovascular disease. A total of 26 ureters were lysed: 25 of the kidneys functioned post-operatively, the one non-functioning kidney having been non-functioning pre-operatively. Relief of obstruction, as judged by improvement in renal function and by pyelographic improvement, was satisfactory. Post-operative complications were few: one of the pyelostomies leaked after the tube was removed, and one patient had a leak arising from ureteric necrosis which required excision and re-anastomosis. During the ureterolysis 2 ureters were perforated, but were successfully managed by local omental wrapping and nephrostomy. Although the histological appearances were non-specific, all biopsies showed fibrosis with inflammatory cells both throughout the tissue and in discrete foci. The histological appearances were classified into 3 groups according to the intensity of the inflammatory reaction as illustrated in Figure 1. Of our last 9 patients 3 fall into each of these categories. Figure 2 is taken from the same patient as Figure 1c after a period of 3 months' treatment with prednisone 15 mg daily. There is a striking reduction in the inflammatory cells, but the mature fibrous elements are unaffected. He had had a laparotomy for suspected malignant disease at which the first biopsy

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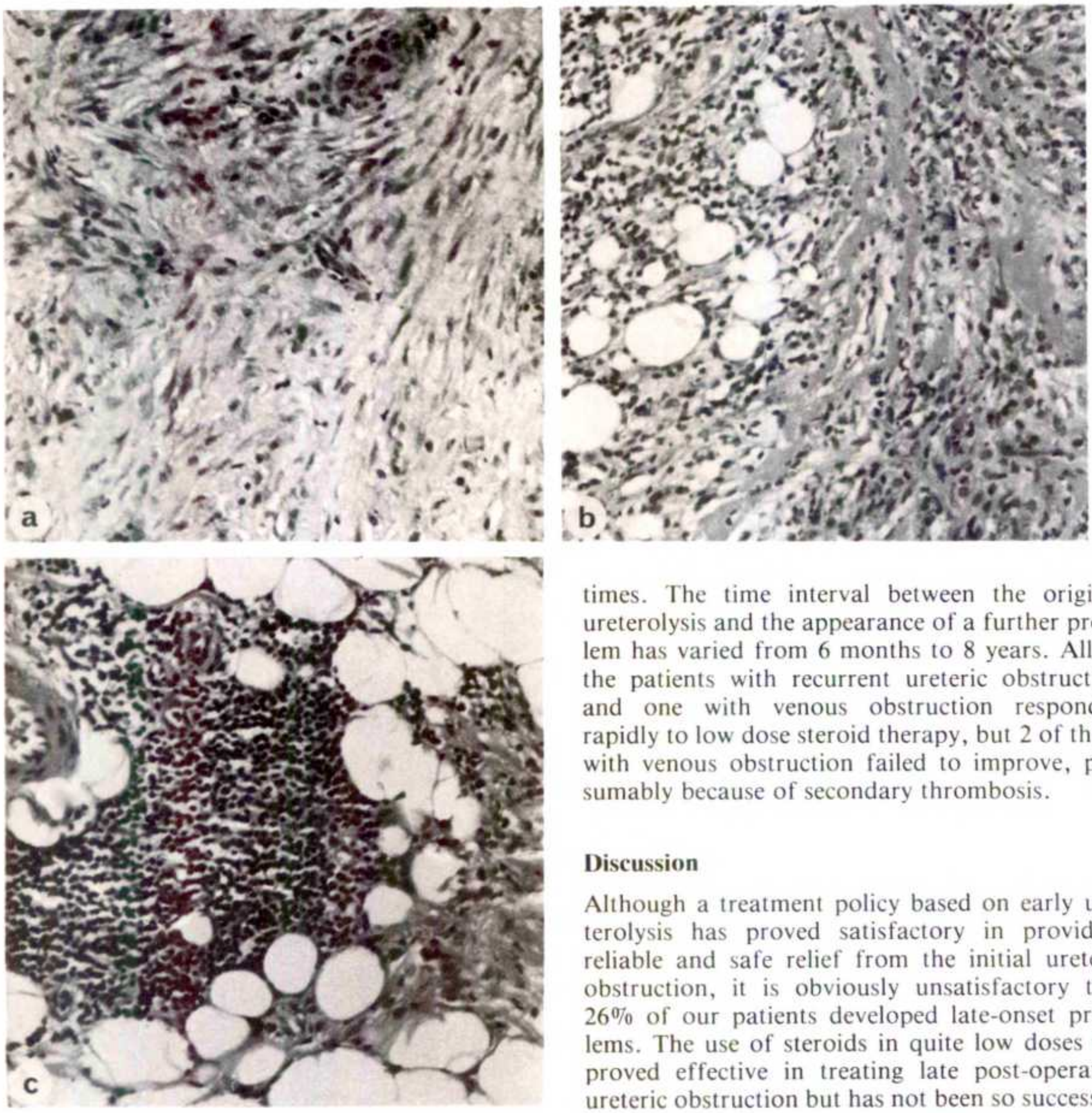

Fig. 1 Histological appearances of retroperitoneal fibrosis graded by cellularity and degree of inflammatory infiltrate. (a) Grade 1, (b) Grade 2, (c) Grade 3 (H and E × 125).

was taken. The second biopsy was taken at bilateral ureterolysis 3 months later, the degree of ureteric obstruction being unchanged on steroids. The ureterolysis he eventually underwent was neither easier nor more difficult than others in our series.

Five patients (4 male, 1 female) presented after surgery with problems arising from extension of their retroperitoneal fibrosis: 3 had venous obstruction and 3 had recurrent ureteric obstruction, one patient having both of these but at different times. The time interval between the original ureterolysis and the appearance of a further problem has varied from 6 months to 8 years. All of the patients with recurrent ureteric obstruction and one with venous obstruction responded rapidly to low dose steroid therapy, but 2 of those with venous obstruction failed to improve, presumably because of secondary thrombosis.

Discussion

Although a treatment policy based on early ureterolysis has proved satisfactory in providing reliable and safe relief from the initial ureteric obstruction, it is obviously unsatisfactory that 26% of our patients developed late-onset problems. The use of steroids in quite low doses has proved effective in treating late post-operative ureteric obstruction but has not been so successful

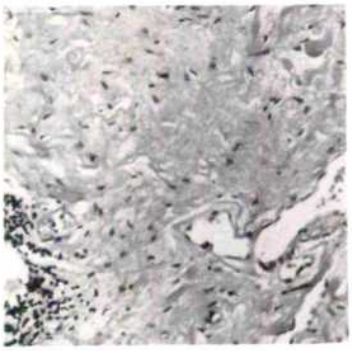

Fig. 2 The same patient as in Figure 1c after 3 months' treatment with steroids 15 mg daily (H and E × 125).

in venous obstruction. The evidence presented by the patient illustrated in Figure 1c and Figure 2 suggests that therapy with steroids can influence favourably the inflammatory element of the disorder but will do little to help a ureter which is deeply embedded in mature fibrous tissue.

The only laboratory test which has been consistent in these patients is the ESR, which is often very strikingly raised. It seems probable that elevation of the ESR reflects the activity of the inflammatory part of the disorder, and may be associated with the process of laying down new plaques of fibrosis.

Charlton (1968) recommended that in patients on treatment with steroids, return of the ESR to normal was an indication for treatment to be stopped, and Ross and Goldsmith (1971) recommended that a persistent rise in the ESR was an indication for steroid treatment to be started.

In the further care of patients with idiopathic retroperitoneal fibrosis, after initially successful surgery to relieve the ureteric obstruction, regular estimation of the ESR seems wise, and the advisability of giving steroids when that measurement is raised must be considered.

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✓ Evaluating Bilharzial Ureteropathy for Surgery

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Summary—In a study of 115 ureters showing chronic bilharzial changes, 4 main patterns of ureteropathy are defined. Type A is benign, shows mild fusiform dilatation localised to the distal ureteric segment and requires no surgery. Type B presents with distal ureteric stricture, without extensive fibrosis, is rare, and shows good results following resection and ureterovesical reimplantation. Type C shows extensive bilharzial changes without stricture and is difficult to evaluate unless fluoroscopy is added to standard urographic investigation. If peristaltic dysfunction is severe, these ureters will require replacement with an ileal segment. Type D ureteropathy presents with fixed tortuosity, mainly in the upper ureteric segment, and conservative surgery, involving freeing and straightening the entire ureter, has shown good results. Staging the presenting ureteropathy has proved valuable in evaluation and follow-up.

Schistosomiasis affects 8% of the world's population and, nowadays, not all of those afflicted are confined to endemic regions. Patients with the late effects of the disease who are seen in Abu Dhabi have come mainly from Egypt but also from endemic areas in Oman and South Yemen.

The mortality associated with urinary bilharziasis is due not only to malignant change in the bilharzial lower urinary tract, but also to the insidious onset of renal failure resulting from severe obstructive disease of the ureters. The former, once recognised, poses few problems in evaluation for radical treatment. It is often difficult, however, to decide upon a line of treatment for the patient who presents with extensive bilharzial involvement of the ureters, together with evidence of progressive renal damage.

A variety of surgical procedures has been described for the management of bilharzial ureteropathy and many of these have provoked conflicting opinion. Honey and Gelfand (1960) reported some success with endoscopic dilatation or ureteric meatotomy in management of the low bilharzial stricture and showed that the ensuing vesicoureteric reflux produced no ill-effects on the kidney for periods up to 20 years. However, not many agree that endoscopic instrumentation is particularly effective in treating the low stricture and there is always the risk of adding post-operative superadded infection to an already damaged urinary tract. Moreover, few are confident that reflux, albeit sterile, is entirely without effect on an already damaged, chronically obstructed kidney.

Some of the unrewarding results seen after resection and reimplantation of the distal ureter for bilharzial stricture may be due to the difficulty experienced in defining the true cause of the dilatation seen on standard intravenous

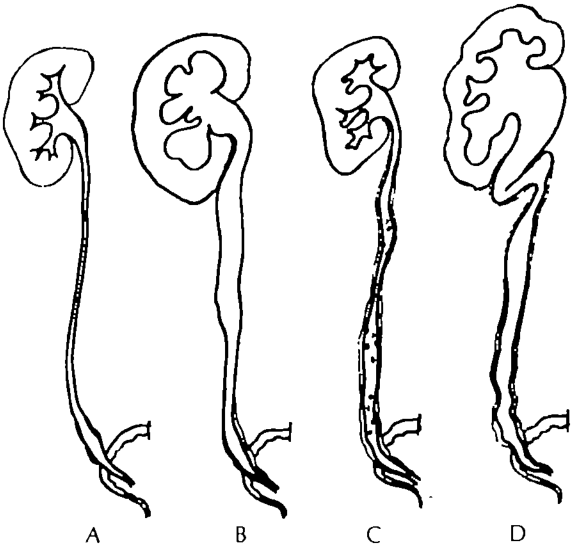

Fig. 1 Bilharzial ureteropathy—A: Minimal changes localised to the lower ureteric segment; B: Stricture, stone or atony in the lower ureteric segment causing significant dilatation of the upper tract; C. Extensive mural and periureteric bilharzial change, without tortuosity or stricture; D: Extensive bilharzial change, with fixed tortuosity of the upper ureter, and stricture or stone.

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urography. Umerah (1977) has shown that in many of these chronically diseased ureters the true cause of the dilatation seen is due to hypotonia or atony of the ureter due to the dense fibrotic change in the wall of the ureter and in the periureteric tissues. The only effective treatment for these ureters is replacement with an ileal segment, a procedure with a high incidence of early complications.

In a previous study (Kinare *et al.*, 1980), we attempted to correlate clinical, radiological and radioisotope evaluation of bilharzial uropathy and to evolve a method of staging the disease. We now present the ureteropathy in 58 patients, with emphasis on the patterns of presentation and indications for surgery in each stage.

Patients, Methods and Results

One hundred and fifteen ureters, in 58 patients with proven urinary bilharziasis, were studied by intravenous urography and radioisotope renography and renal scanning. Wherever the ureter appeared extensively involved in bilharzial fibrosis, fluoroscopy was added to the standard intravenous urography. In a few instances, retrograde ureterograms were performed to outline suspected regions of stricture that remained poorly visualised on urography or isotope scanning. Nuclear studies were performed using ^{99m}Tc DTPA or DMSA for the dynamic renal scans and renograms.

Each diseased ureter was evaluated separately, the degree of bilharzial involvement and dysfunction assessed and staged into one of the 4 main patterns recognised (Fig. 1).

Of the ureters studied, 24.6% showed bilharzial changes confined to the distal segments and these appeared mainly as a localised, fusiform dilatation and without abnormality of the upper tract (Fig. 2a). From serial urography in one patient over a period of 11 years, it was seen that this form of ureteropathy runs a fairly benign course and that surgery is unlikely to be necessary.

True stricture of the distally involved ureter, without changes of fibrosis in the upper segment, is a rare finding (Type B) and was seen in only 5 cases. This type of upper tract dilatation is smooth and resolves completely following resection of the distal strictured ureter and ureterovesical reimplantation.

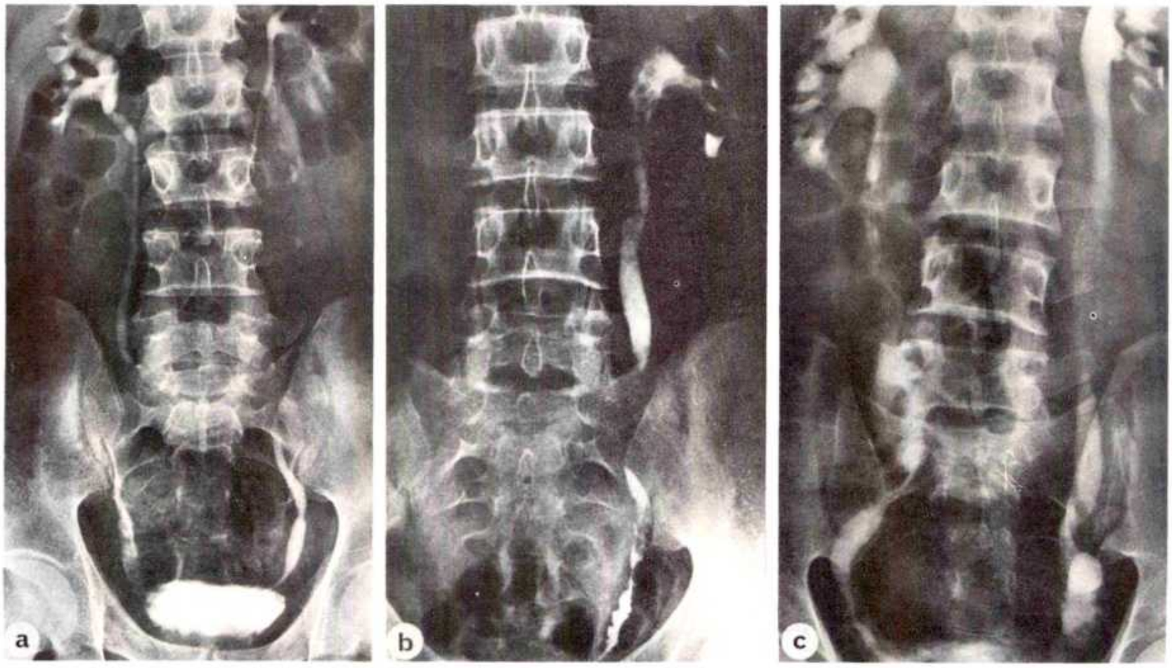

Fig. 2 Bilharzial ureteropathy: (a) IVU showing Type A changes, confined to the lower ureters, with marked ureteritis cystica on the right side; (b) emptying phase of retrograde pyeloureterogram displaying extensive ureteropathy and marked cystic change in the pelvis and upper ureter (Type C). In spite of the ragged appearance of the distal ureter, there was no significant hold-up to drainage (this is the same patient displayed in Fig. 3). (c) Extensive bilateral bilharzial fibrosis without, however, significant delay in emptying, in spite of a mild degree of dissociated peristalsis seen on fluoroscopy. Surgery would not immediately be indicated in any of the above cases, although serial urography and careful review would be expected in case C.

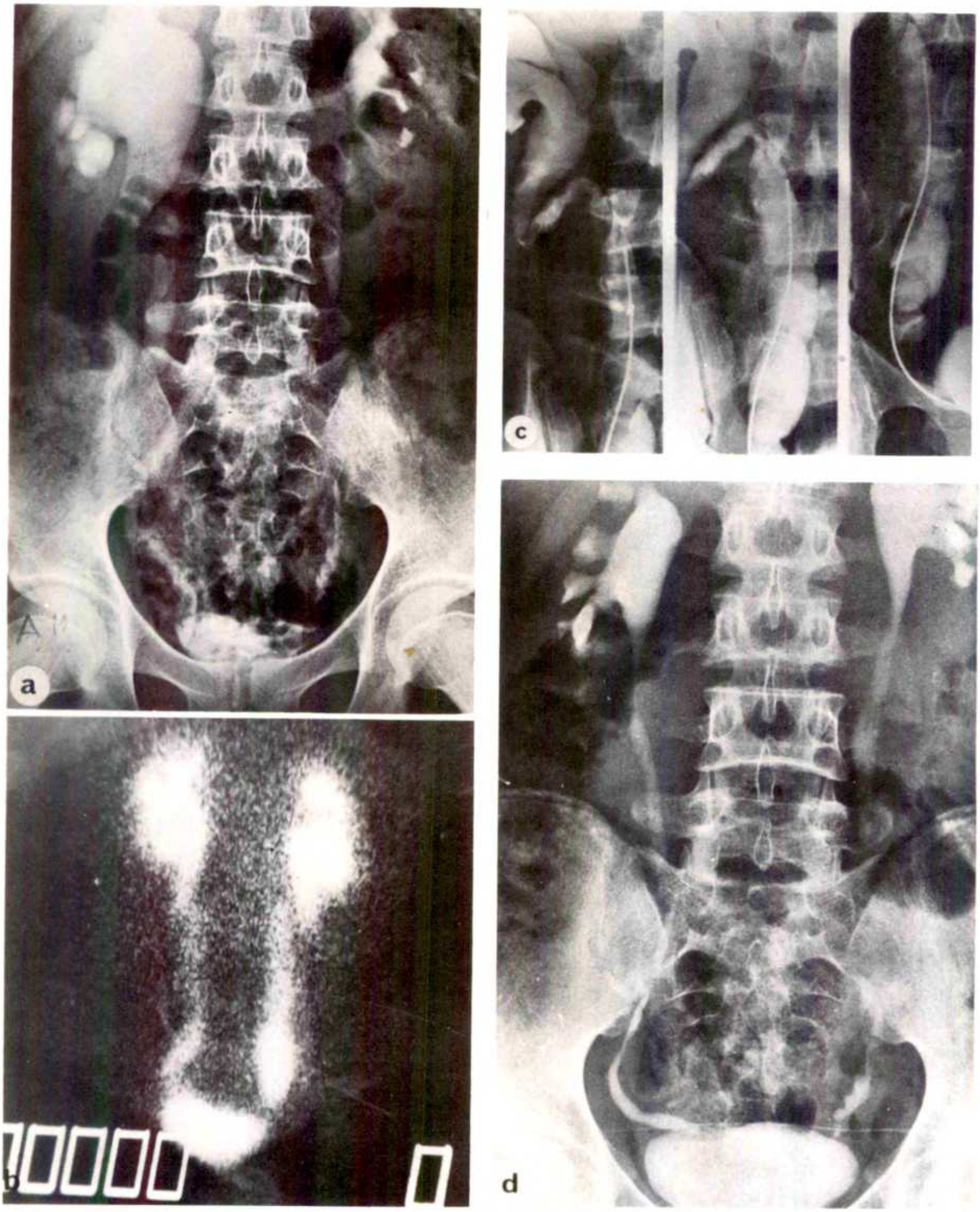

Fig. 3 Type D bilharzial ureteropathy of the right tract, indistinctly visualised on intravenous urography (a), but clearly evident on DTPA scanning (b) and confirmed by right retrograde ureterography (c). At surgery, the entire ureter was freed and straightened, and the distal ureter reimplanted without excising the grossly fibrosed terminal segment. At 3-month follow-up intravenous urography (d) there appears satisfactory improvement in drainage of this tract.

Almost half of the total number of ureters evaluated showed extensive involvement of the ureter with fibrosis but without evidence of stricture. These ureters were thick-walled (Fig. 2c) and sometimes were hypotonic or showed dissociated peristalsis or reflux. Ureteric dilatation is often significant but if the post-micturition urograph film shows satisfactory emptying of the upper tract, surgery should be withheld. This pattern of bilharzial ureteropathy (Type C) requires careful serial review and, if deterioration becomes evident on urography or isotope renography, the only means of salvaging the upper tracts is by total replacement of the ureter or by permanent urinary diversion. Wallace (1979) has reported good results with ileal replacement of the heavily involved bilharzial ureter, but the long-term results and prognosis are still unknown.

The commonest complication in Type C bilharzial ureteropathy was the development of a ureteric stone, but almost one-third of these, regardless of size, showed spontaneous passage down into the bladder. In the 2 cases where a simple ureterolithotomy was performed, there was no evidence of distal ureteric stricture. None of the patients in this series showed reflux severe enough for surgery to be considered.

Type D bilharzial ureteropathy was a well defined pattern. There is heavy involvement of the ureter in fibrosis, with poor visualisation on intravenous urography and marked renal cortical atrophy. There is gross dilatation and tortuosity, particularly in the upper ureteric segment where a "fixed" kink appears to be a constant feature. This region of the ureter (opposite the third lumbar vertebral transverse process) not infrequently shows involvement during the primary bilharzial infection, probably due to shunting of ova through local porto-systemic venous communications (Chapman, 1966). Undoubtedly, this fixed loop is obstructive, although these ureters also present as a relative stricture in the distal segment (Fig. 3).

Table Surgical Procedures Required for Bilharzial Ureteropathy in 58 Patients (115 Ureters)

	Advised	*Performed*
Ureteric meatotomy (endoscopic)	2	2
Ureteric dilatation (open, with splinting drainage)	(3)	3
Ureterolithotomy only	3	2
Ureterolysis only (with splinting drainge)	(4)	4
Resection of lower ureteric segment and reimplantation		
Into bladder	5	3
Into Boari flap	2	1
Resection of upper ureteric stricture (and stone removal)	2	2
Resection, straightening and reimplantation	12	7
Ureteric replacement	4	—
Total	37	24

Seven of the ureters showing Type D changes were subjected to an extensive mobilising and straightening procedure, following which the straightened upper segment was divided just proximal to the heavily fibrosed distal segment and reimplanted into the bladder. In all cases there was sufficient ureteric length for a short tunnel reimplant. The fibrous distal segment was closed off and left *in situ* in 4 cases, without ill-effect. Two of these 7 cases have shown extremely good results, one proved unsatisfactory and the rest were lost to follow-up.

The results of surgical evaluation of the ureters, in this series, are shown in the Table. One-third of the ureters required surgery, although not all of these finally came for operation. Ileal replacement of the diseased ureter was indicated in 4 instances, but none of these patients consented to the procedure and all were lost to review when they returned home to Egypt.

Discussion

Although the effects of schistosomiasis on the urinary tract have been extensively described in the literature, the natural history of some of the more severe forms of ureteropathy presenting in the "burnt-out" stage of the disease is not yet clear. Moreover, the true nature of the obstruction accounting for dilatation of the upper tracts is not always evident from standard intravenous urography. Contrary to wide belief, stricture of the bilharzial ureter is a relatively rare occurrence and it is not surprising therefore that many attempts to relieve the ureteric dilatation seen, by various methods of lower ureteric surgery, prove so unrewarding.

The presence of stone in the bilharzial ureter should not necessarily suggest that a distal stricture is present. Saad and Hanafy (1974) have suggested that many of these calculi are caused, not by chronic stasis, but by crystalloids being trapped in areas of cystic change in the ureteric epithelium. These then grow and are shed into the ureteric lumen as calculi.

Staging ureteropathy has been found to be of practical value not only in evaluating the disease for surgery, but also in assessing post-operative results and in serial follow-up of those patients where a watching policy is decided upon.

Acknowledgements

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Urinary Ascites in the Newborn

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Summary—Seven cases of neonatal urinary ascites secondary to obstructive uropathy are reported. In 2 the bladder had perforated; in 4 there was perirenal extravasation; in 1 the site of leakage was not determined. A localised parenchymal perforation was found in 3 kidneys.

Treatment was by temporary urinary diversion followed by operative relief of the obstruction. Six patients survive in good health; 1 infant died from causes unrelated to the ascites or the urinary tract. It is suggested that spontaneous urinary tract perforation with the development of ascites is often beneficial in the long term since it decompresses the obstructed system and lessens renal parenchymal damage.

The first description of fetal ascites has been ascribed to Mauriceau in 1681 (Wynne *et al.*, 1968). In 1837, King described a fetus with ascites and a dilated urinary tract secondary to urethral atresia. It was not until 1952 that the first successfully treated case of neonatal urinary ascites was reported by James and Davis. The mortality rate of the condition remained high and was reported in 1972 to be 70% (Thompson and Bruns). Urinary ascites has been described as occurring in infants with an apparently normal urinary tract as a consequence of spontaneous perforation of the bladder (Griscom *et al.*, 1977; Murphy *et al.*, 1978). However, most cases have been the result of an obstructive lesion, the site of which has varied. The present article records our experience with 7 cases.

Patients

Between 1956 and 1979, 7 infants (6 boys and 1 girl) with urinary ascites secondary to urinary obstruction were admitted to Alder Hey Children's Hospital, Liverpool. The ages at presentation ranged from birth to 3 weeks. The obstructive lesions were posterior urethral valves (3), anterior urethral valve (1), pelviureteric junction stenosis in a solitary kidney (1), bilateral obstructed megaureters (1), and neuropathic bladder (1) (Table 1).

The site of urinary extravasation was determined in 6 of the 7 cases. Although the upper urinary tract was the most common site, occurring in 4 patients, 2 developed ascites secondary to intraperitoneal rupture of the bladder. The latter occurred in a male infant with posterior urethral valves and in a female with a neuropathic bladder due to a myelomeningocele. Of the 4 patients with perirenal extravasation, 3 kidneys at surgery were seen to have a discrete parenchymal perforation. In the other it appeared that the leakage was from a caliceal fornix. In no case was there a perforation of the peritoneum overlying the kidney.

The initial form of management of the 7 patients was temporary urinary diversion. Suprapubic tubes were used for the 2 bladder perforations which were closed at the same procedure. In the patients with upper tract extravasation, nephrostomy tubes were placed in all except one who underwent a loop cutaneous ureterostomy. Two patients had initial paracentesis with subsequent diversion.

Six of the 7 patients are alive and well. The one death occurred in the girl with a ruptured neuropathic bladder who died of meningitis secondary to repair of her myelomeningocele. In

Table 1 Urinary Ascites

Case	*Aetiology*	*Site of extravasation*
1. L.H.	Posterior urethral valves	Left kidney
2. S.M.	Posterior urethral valves	Left kidney
3. K.B.	Posterior urethral valves	Bladder
4. M.G.	Anterior urethral valves	?
5. M.L.	Pelviureteric junction obstruction (solitary kidney)	Left kidney
6. M.S.	Bilateral obstructed megaureters	Left kidney
7. S.C.	Neuropathic bladder	Bladder

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the 4 cases with leakage of urine from the kidney, renal function in the involved kidney was maintained and subsequent renal growth was satisfactory. Contralateral nephrectomy was required in one boy with posterior urethral valves because of non-function with renal dysplasia.

Discussion

It has been estimated that urinary ascites accounts for approximately 25% of all cases of neonatal ascites (Colodny and Griscom, 1978). However, it must be said that in all large series of neonatal ascites there was an appreciable number of cases in which the underlying pathogenesis could not be determined (Griscom *et al.*, 1977).

In the diagnosis of urinary ascites, intravenous urography may demonstrate local extravasation of contrast either in the perirenal area or beneath the renal capsule (Dockray, 1965; Barry *et al.*, 1974). If the contrast material reaches the peritoneal cavity, the relative radiolucency of the liver may be helpful (Colodny and Griscom, 1978). Cystourethrography is required to visualise the posterior urethra and to determine if there is vesicoureteric reflux or bladder rupture. Blood urea nitrogen will usually be elevated, enhanced by the absorptive qualities of the peritoneum. Aspiration of the peritoneum and analysis of the ascitic fluid will exclude chylous and bilious ascites, but biochemical investigation may be misleading in cases of urinary ascites since the ascitic fluid equilibrates with the serum.

Lord in 1953 proposed that the urine reached the perirenal space by transudation. Moncada *et al.* in 1968 demonstrated urine leaking from the renal fornix into the perirenal area and thence into the peritoneal cavity. This progression explains the presence of perirenal urinomas that may or may not progress to frank ascites. Garrett and Franken in 1969 reported 3 patients with posterior urethral valves who developed large perirenal accumulations without ascites. In each case, the parietal wall of the cyst was renal capsule and this prevented the escape of urine and subsequent intraperitoneal collection. In our experience, one boy with posterior urethral valves presented with a flank mass and needle aspiration and injection of contrast confirmed the presence of a perirenal urinoma without ascites. In none of our cases with

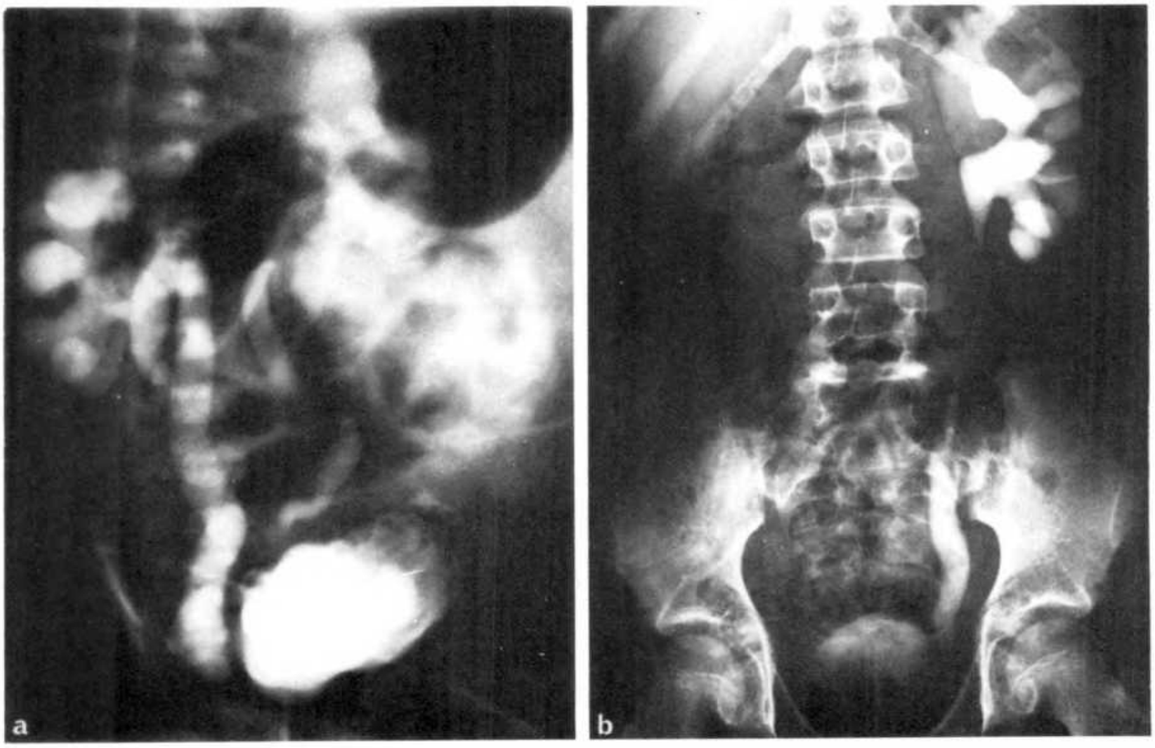

Fig. 1 Urinary ascites in boy with urethral valves. (a) Cystogram at age 2 days. Bilateral reflux with perirenal extravasation on left. (b) IVP at age 11 years. Right nephrectomy for non-function. Left kidney shows mild hydronephrosis.

perirenal extravasation was there a perforation in the overlying parietal peritoneum. It must be presumed that the urine enters the peritoneal cavity by a process of diffusion, a phenomenon which appears to be peculiar to the perinatal infant since it is not encountered in the older child or the adult.

Many authors have stated that it is unusual to find a distinct site of leakage from the kidney into the perinephric space. In this series, excluding the 2 perforated bladders, the urinary ascites could be localised to an individual kidney in 4 of 5 patients. In 3 of these a definite parenchymal perforation was identified. It is of interest that in these patients, the original intravenous urogram demonstrated better function and less morphological abnormality in the perforated kidney than in the non-perforated one. In one case of posterior urethral valves the initial intravenous urogram demonstrated no function in the right kidney, and left hydronephrosis. Cystography showed bilateral reflux with perirenal extravasation on the left (Fig. 1a). Surgical exploration revealed a parenchymal perforation in the left kidney; nephrostomy drainage preceded endoscopic valve fulguration. The patient subsequently had his non-functioning right kidney removed. Follow-up intravenous urography 11 years later demonstrated that the left kidney, the original perforated one, had some hydronephrosis but was growing well (Fig. 1b). The initial intravenous urogram of the patient with bilateral obstructed megaureters demonstrated significantly better function in the left, perforated kidney than in the right non-perforated kidney (Fig. 2a). The patient underwent resection of the distal ureters with reimplantation to the bladder; post-operative intravenous urography at 3 months revealed prompt function bilaterally with improvement of the hydronephrosis (Fig. 2b). It is likely that the rupture of the collecting system and intraperitoneal diffusion protects the kidney from further hydrostatic damage. By contrast, our patient with perirenal urinoma without ascites had severe kidney damage and died of renal failure at the age of 3 years. In his case it appeared that failure of the urinoma to communicate with the peritoneal cavity did not adequately decompress the urinary tract and allowed irreversible kidney damage to occur.

Review of the literature produced 92 cases of documented urinary ascites; Table 2 illustrates the underlying pathogenesis. Our series correlates

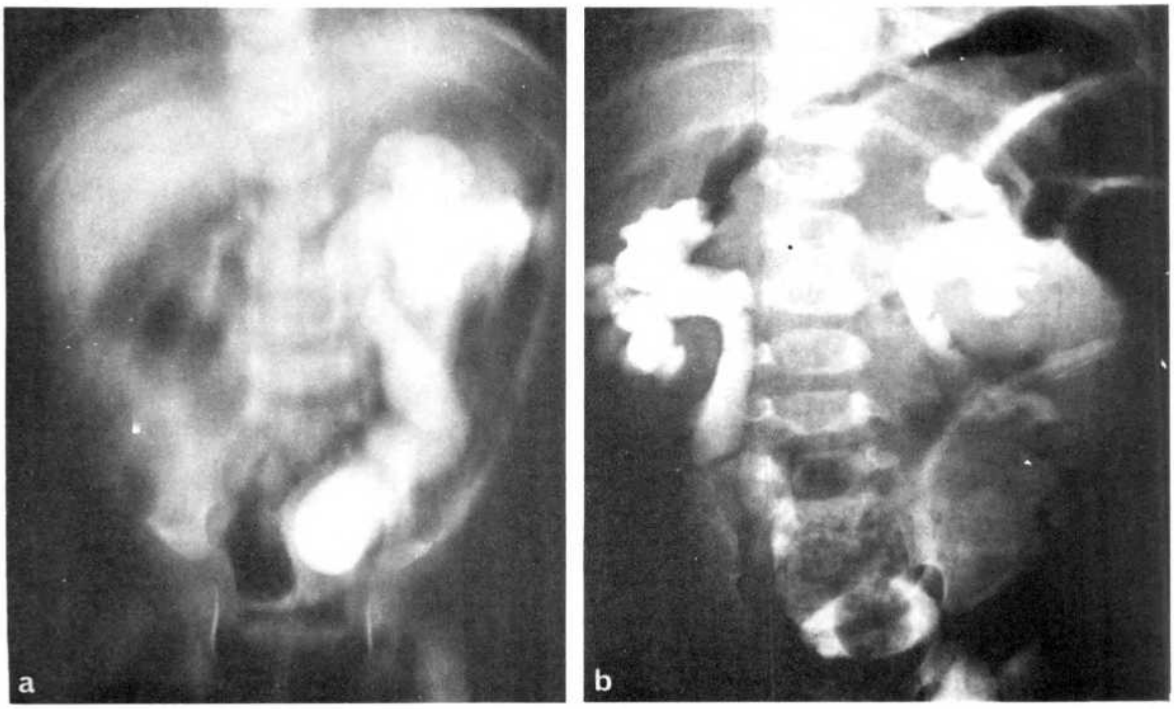

Fig. 2 Urinary ascites in boy with bilateral obstructed megaureters. (a) IVU before surgery. Poor concentration on right. Hydroureteronephrosis on left with perirenal extravasation. (b) IVU 3 months after bilateral ureteric reimplantation. Improved appearance bilaterally.

Table 2 Urinary Ascites—Aetiology

Posterior urethral valves	52
Spontaneous bladder rupture	8
Urethral atresia	5
Neuropathic bladder	5
Bladder neck obstruction	4
Pelviureteric junction obstruction	3
Anterior urethral valve	2
Ureterocele	2
Obstructed megaureter	2
Other	9
Total	92

well with the literature in that one half of the cases were due to lesions other than posterior urethral valves.

The mortality rate with urinary ascites has been reported to be as high as 70% (Thompson and Bruns, 1972). The mortality in this series was significantly lower, with only one death which was not related to the urinary ascites nor the underlying uropathy. Our experience agrees with that of other authors that, in cases of urinary ascites, prompt decompression of the urinary tract by temporary diversion followed by relief of the underlying obstruction is the key to successful management. The long-term prognosis, however, depends upon the severity of renal damage which has occurred prior to presentation.

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Endoscopic Biopsy in the Diagnosis of Peripheral Denervation of the Bladder

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Summary—Endoscopic biopsies of the bladder were stained using a simple neurohistochemical technique to demonstrate the normal cholinergic innervation. The same technique was used on patients in whom a peripheral neuropathic bladder was suspected and clear evidence of denervation obtained.

It is suggested that the technique be applied to all cases where peripheral denervation is a possibility to assist in diagnosis and to select cases where long-term urological follow-up is mandatory.

Peripheral denervation of the bladder may arise as a result of radical pelvic dissection either for carcinoma of the rectum or as part of an extended hysterectomy for malignant disease. Diagnosis is often difficult and usually depends upon the interpretation of urodynamic data—in particular, the change in configuration of the cystometrogram and the absence of a co-ordinated voiding reflex. The cystometric abnormality commonly recorded shows a hypertonic systolic pattern, but this may be found in other conditions. Elicitation of a voiding reflex may be difficult in the conditions of urodynamic testing, even if the patient's bladder is normally innervated, so that reliance on standard urodynamic investigation to diagnose peripheral denervation of the bladder must be limited.

The phenomenon of denervation supersensitivity to exogenous cholinergic stimulation of the bladder has been used as a diagnostic test (Lapides *et al.*, 1962; Glahn, 1970). The intravesical pressure of the denervated bladder is seen to increase following a subcutaneous injection of bethanechol or carbachol. The response is measured either as a shift to the left of a repeated cystometrogram or by continuously recording the change in intravesical pressure at a fixed volume. If positive, the test provides only presumptive evidence of denervation, whilst a negative result does not exclude bladder neuropathy. Finally, the result may be equivocal and inconclusive.

Objective evidence of bladder denervation is needed to make an accurate diagnosis and we have investigated the use of bladder biopsies for this purpose. The study was designed, firstly, to establish whether endoscopic biopsy material was adequate to demonstrate the normal cholinergic innervation of the bladder using a standard neurohistochemical staining method and, secondly, to determine whether the method was appropriate to diagnose denervation of the bladder.

Patients and Methods

Twenty-five patients were included in the study.

The first 9 were all patients with normal bladder function undergoing endoscopic examination for a variety of reasons.

The remaining 16 were patients who had had an abdominoperineal excision of the rectum 4 months to 5 years previously. There were 15 males and 1 female, mean age 68 years (range 52-84). Detailed urodynamic data were available on 8 of these patients, whilst 8 did not have lower tract dynamic studies.

Muscle biopsies of the bladder were taken with a standard 24 FG irrigating resectoscope. Where possible they were taken across a trabeculated muscle bundle to include mucosa, submucosa and muscle. Three sites were chosen: each lateral wall of the bladder and the trigone.

When biopsies were taken from a patient who had had an abdominoperineal excision, a sample of normal detrusor from another case was taken at an endoscopic procedure on the same operating list, to serve as a control. These specimens were

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stained and examined simultaneously with the test biopsy material.

Histochemical Technique

The staining method used to identify the cholinergic innervation of the bladder muscle was the direct colouring technique for cholinesterases described by Karnovsky and Roots (1964). The method can be made specific for acetylcholinesterase (El Badawi and Schenk, 1967), using a non-specific esterase inhibitor (isopropylpyraphosphamide), but this modification of the technique was not used because of the extreme toxicity of the inhibitor. The procedure and incubation medium, based on acetylthiocholine iodide (Sigma Chemicals), was otherwise similar to that described by El Badawi and Schenk (1967).

Fresh bladder biopsies were frozen in isopentane cardice (or liquid nitrogen), and 15 μ sections were cut on a cryostat at $-30°C$. These were fixed in ice-cold neutral formalin for 20 min, then washed and incubated for 1 h at 37°C in the staining medium. Nuclei were counterstained in Harris haematoxylin for 30 s and, after washing, the sections were dehydrated, cleared and mounted in synthetic mounting medium.

The sections were examined under phase contrast microscopy and the cholinergic fibres, often varicose in appearance, were readily identified because of precipitation of a red-brown stain complex along their length, indicating the maximum concentration of cholinesterase activity.

Results

The normal innervation of the detrusor can be seen in Figure 1, where there appear to be 2 sets of easily identifiable fibres: the first are in the submucosa and are presumably sensory fibres, and the second group can be seen interspersed between the muscle bundles. This pattern of innervation was seen in each of the first 9 normal cases examined. Similar appearances were also found in each of the control biopsies, allowing valid conclusions to be drawn from the test biopsy material.

No significant difference of innervation was seen when comparing biopsies taken from the trigone with those taken from the lateral walls. The orientation of the muscle bundles seemed more uniform in the trigone, where both the muscle bundles and nerve fibres were more often found in cross section.

Figure 2 was taken from a case 18 months following an abdominoperineal excision of the rectum

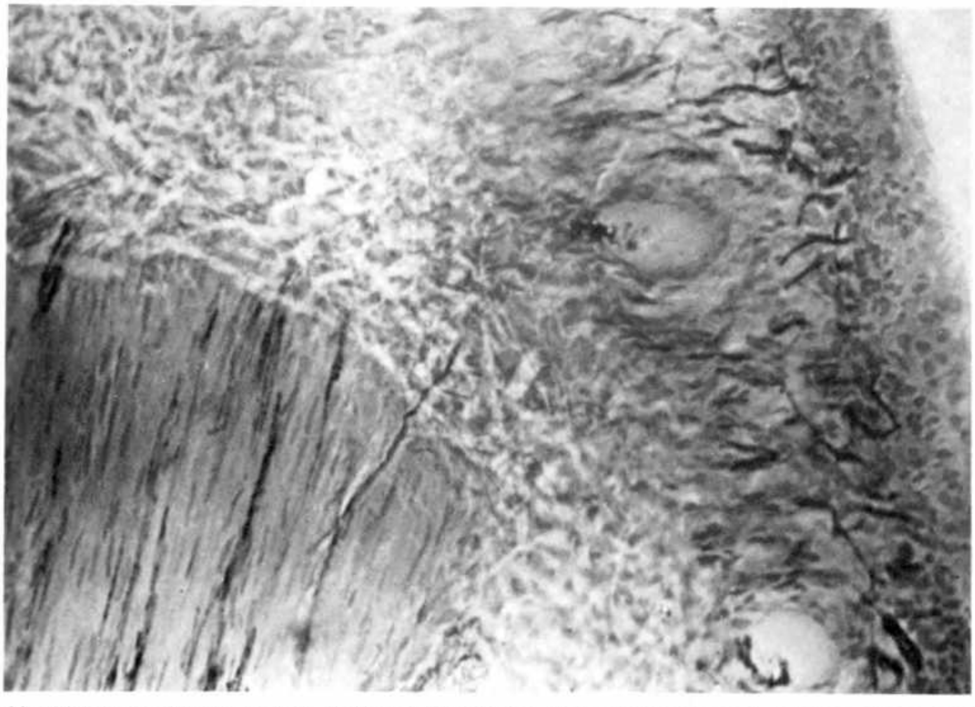

Fig. 1 Bladder biopsy showing the normal cholinergic innervation of the submucosa and detrusor. Phase contrast photomicrograph (× 125).

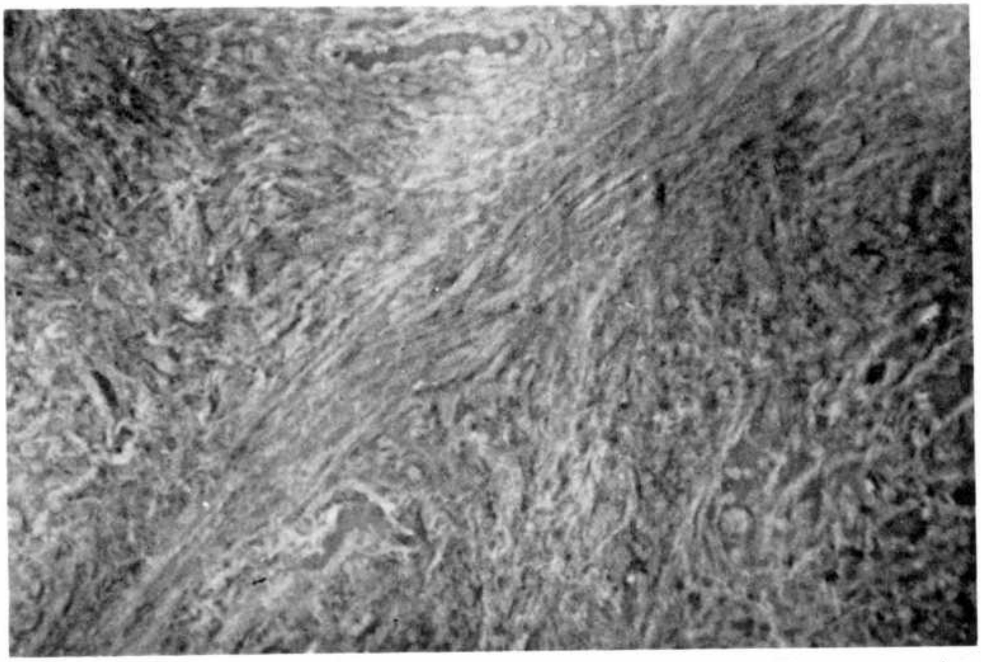

Fig. 2 Detrusor biopsy of the bladder 18 months after an abdominoperineal excision. Phase contrast photomicrograph (×125).

in which a neuropathic bladder was suspected on urodynamic investigation, including denervation supersensitivity testing. No nerve fibres are visible in the bladder muscle.

Figure 3 shows the result obtained immediately before and 8 months after an abdominoperineal excision of the rectum. The normal cholinergic innervation found pre-operatively has disappeared in the post-operative specimen.

Table 1 shows the correlation between urodynamic data suggesting denervation, denervation supersensitivity testing and neurohistological evi-

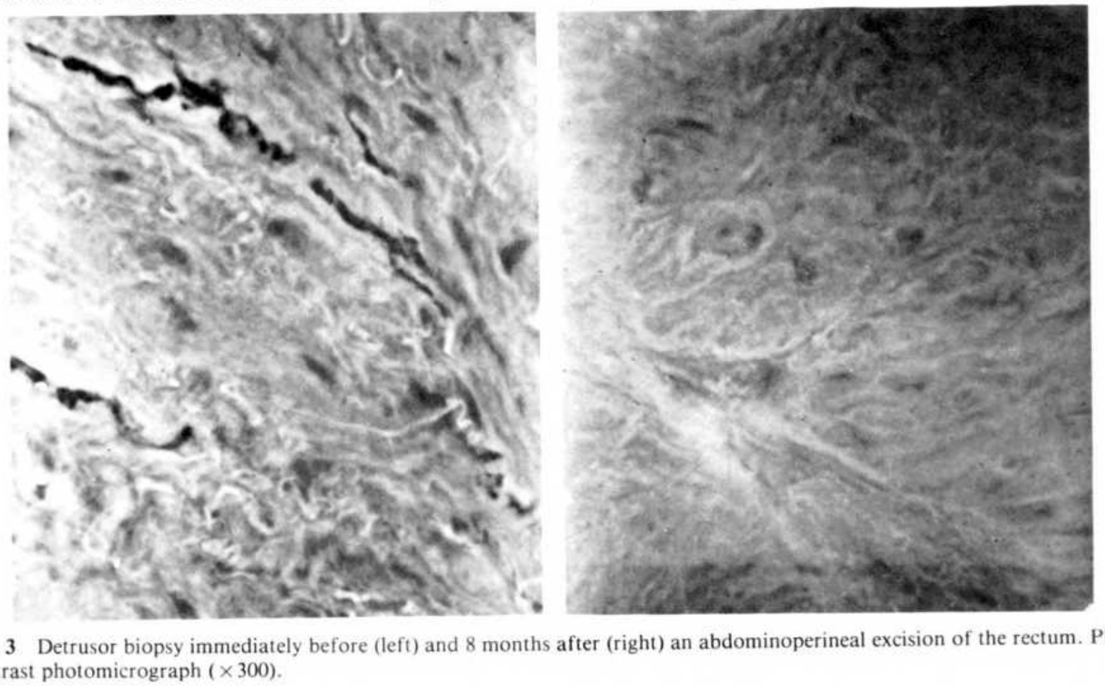

Fig. 3 Detrusor biopsy immediately before (left) and 8 months after (right) an abdominoperineal excision of the rectum. Phase contrast photomicrograph (×300).

Table 1

Patients	*Cystometrogram*	*Voiding reflex*	*Denervation supersensitivity* (Increase in intra-vesical pressure following bethanechol 2.5 mg S.C. cmH_2O)	*Neurohistology*
1	Hypertonic	Negative	Positive (20)	Negative
2	Hypertonic	Negative	Positive (29)	Negative
3	Uninhibited Normotonic	Positive (obstructed)	Negative (5)	Positive
4	Hypertonic	Negative	Positive (18)	Negative
5	Hypertonic	Negative	Positive (15)	Negative
6	Hypertonic	Negative	Positive (42)	Negative
7	Hypertonic	Negative	Positive (32)	Negative
8	Hypertonic	Negative		Pos/Neg.

dence of denervation. In 6 of the 7 cases where denervation was suspected the endoscopic biopsy technique showed there to be no nerve fibres present in the bladder muscle, whilst in one case (No. 3), where bladder function was maintained and supersensitivity testing negative, a normal pattern of innervation was found. In all but one case, when denervation was found on the biopsy specimens, the 3 specimens from the bladder showed similar appearances in each section examined. However, in one case (No. 8) in which the bladder function studies suggested denervation, cystoscopy showed gross trabeculation involving only the left half of the bladder, with a normal appearance on the right. Biopsies taken from each side showed normal innervation on the right but a complete absence of nerve fibres in the sample from the left side of the bladder—the side with gross trabeculation.

Of 8 patients who did not have lower tract function studies, 3 were found to have normal bladder innervation on endoscopic biopsy and 5 had no detectable cholinergic innervation (Table 2).

Discussion

Neurohistochemical staining of bladder biopsies is a simple method of obtaining objective evidence of bladder denervation. Only a small piece of bladder muscle taken with a resectoscope is required. Tissue damage due to heat at the periphery of the specimen has not proved to be a problem, nor has the omission of non-specific cholinesterase inhibition from the histochemical method. The diagnosis of denervation is, in fact, assisted by the profound depression of cellular background cholinesterase activity in those cases with absent cholinergic innervation to the muscle. Normal innervation can be recognised without difficulty using light microscopy, but scrutiny of the sections under phase contrast conditions helps the recognition of nerve fibres, and will allow a diagnosis of denervation to be made with confidence when no nerve fibres are found.

Table 2

Patients	*Neurohistology*
9	Negative
10	Negative
11	Negative
12	Positive
13	Negative
14	Positive
15	Positive
16	Negative

The correlation between the endoscopic biopsy results and the urodynamic data is good in that, with only one exception, when denervation was suggested by the functional studies the biopsy result showed no nerve fibres to be present in the bladder muscle. In one case, however, part of the bladder innervation was found to be preserved despite a urodynamic diagnosis of denervation. This bladder had gross trabeculation on one side only and the muscle was denervated on that side, with preservation of normal innervation on the other. This raises 2 interesting points: firstly, that even when the denervation of the bladder after pelvic dissection is partial, normal function may be abolished and therefore any degree of denervation is significant and should be sought; secondly, that there is a close association between denervation and gross trabeculation, so that endoscopic biopsies should be taken from a trabeculated muscle bundle when searching for denervation.

To identify a bladder which is peripherally denervated may be crucial to the management of an individual patient. Usually, urodynamic investigation, with denervation supersensitivity testing, is used to imply the diagnosis. This study has shown that objective evidence of denervation can be obtained using an endoscopic biopsy method to confirm the urodynamic diagnosis. Furthermore, it will readily identify peripheral bladder denervation in patients in whom urodynamic testing is not possible.

It is suggested, therefore, that the technique of endoscopic biopsy should be used to make an accurate diagnosis in all cases where peripheral denervation of the bladder as a result of pelvic dissection is a possibility.

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Urinary Incontinence and Minimal Pyramidal Disease

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Summary—Nine patients with detrusor instability and minimal pyramidal disease are presented. None had neurological symptoms. All had severe urinary symptoms. These patients may add support to the theory that all detrusor instability has a neurogenic basis.

Detrusor instability is one of the well recognised causes of urinary incontinence. Clinically it produces frequency, urgency, nocturia, urge incontinence and bed-wetting. The condition occurs in major neurological disease in both sexes and is associated with bladder outlet obstruction in males. A third group of patients has neither neurological disease nor outlet obstruction, the so-called "idiopathic" group. Neurological lesions which produce detrusor instability are usually located above the sacral cord segments and include spinal cord trauma, dysrhaphic states, tumours, demyelinating diseases, degenerative disease of the nervous system and cerebrovascular disease.

In this paper we describe 9 patients who presented with urinary symptoms related to detrusor instability but who were found to have definite, although asymptomatic, neurological disease. All patients showed evidence of pyramidal disorders, not previously reported, in association with symptomatic detrusor instability. We feel that these patients may represent a link between instability of obvious neurogenic origin and the large group of patients in whom no neurological disease is noted.

Patients

All 9 patients were initially referred to one of us (D.G.T.) for evaluation of urinary symptoms, usually incontinence (Table). They constituted approximately 3% of the total number of patients with instability investigated in the Urodynamic Unit. The presenting symptoms ranged from frequency with minimal urge incontinence to lifelong bed-wetting. All patients had sterile urines with no significant history of urinary tract infections. No patient had haematuria. Intravenous urography was performed in all patients. One patient (J.H.) had a small bladder diverticulum, another showed bladder trabeculation (M.M.) and a third showed what was thought to be a significant volume of residual urine (M.R.). The remaining 6 patients had normal urography.

Urodynamic investigation took the form of pressure/flow studies with synchronous fluoroscopy during both filling and voiding phases. All patients showed marked detrusor instability, often associated with a small bladder capacity and involuntary voiding to completion.

Neurological Findings

All patients were examined independently by a consultant neurologist (G.A.B.D.J.) and were found to have clinical evidence of pyramidal tract disease. All had exaggerated deep tendon reflexes in the lower limbs, several with ankle clonus. All but 2 (M.M. and M.B.) had exaggerated upper limb reflexes. Several patients had extensor plantar responses or positive Hoffmann's reflexes. Three patients had bilateral pes cavus deformities. One patient had minor sensory abnormalities, but the remaining 8 patients had normal sensation and co-ordination. None demonstrated occular or cranial nerve abnormalities, but 2 patients showed evidence of exaggerated reflex activity extending above the cervical cord.

Neurological investigations included lumbar myelography (2 patients), EMI brain scan (4 patients) and electromyography, and all were normal.

Illustrative Cases

Three cases are presented in more detail. The firs represents the patient with the most severe neurological disease, the second a patient in whom th urological symptoms became manifest only afte

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table Details of Patients With Pyramidal Tract Disease

Patient	*Sex*	*Age*	*Symptoms*	*Feet*	*Pyramidal signs*	*Brain stem*
A.F.	F	16	Lifelong frequency, urgency + incontinence	Pes cavus	Upper Lower limbs	+
M.M.	M	18	Incontinence following proctocolectomy	Pes cavus	Lower limbs	–
E.H.	F	38	Severe frequency, urgency + incontinence	Normal	Upper Lower limbs	+
B.B.	F	40	6 years—frequency, urgency + incontinence	Normal	Upper Lower limbs	+
J.H.	F	23	Hesitancy	Normal	Upper Lower limbs	–
J.R.	F	47	5 + years—frequency, urgency + incontinence	Pes cavus	Upper Lower limbs	–
P.B.	M	20	Lifelong eneuresis, frequency, urge incontinence	Normal	Lower limbs	–
B.H.	M	29	Frequency, urgency, nocturia + incontinence	Normal	Upper Lower limbs	+
M.R.	M	9	Frequency, eneuresis, urgency + incontinence	Normal	Upper Lower limbs	+

major pelvic surgery, and the last appears to typify the syndrome.

A.F., a 16-year-old girl, gave a life-long history of severe frequency, urgency and urge incontinence. On close direct questioning she admitted to some walking difficulty with stumbling. General examination was normal but neurological examination revealed exaggerated limb reflexes with finger flexion and positive Hoffmann reflexes bilaterally. There was bilateral blunting of sensation to pinprick in a neuropathic distribution as far as the knees. There was bilateral pes cavus and minimal dorsal scoliosis. Urodynamic studies showed definite detrusor instability with small uninhibited contractions initially, but rising to contractions of 40 cmH_2O pressure at 500 ml bladder capacity. The urinary symptoms were related to the detrusor instability probably due to a form of spino-cerebellar degeneration with some features of Friedreich's ataxia.

M.M., an 18-year-old boy, complained of incontinence on laughing or lifting as well as urgency, enuresis and mild urge incontinence. The symptoms arose following a total proctocolectomy for Crohn's disease 15 months prior to presentation. He denied any urinary symptoms prior to surgery. Erection and ejaculation were normal.

Neurological examination showed exaggerated deep tendon reflexes in the lower limbs with extensor plantars. He had bilateral pes cavus and claw toes. His brother also had bilateral pes cavus but no urinary symptoms.

Urodynamic investigation showed marked uninhibited detrusor contractions and involuntary voiding associated with detrusor-sphincter dyssynergia. The intravenous urogram showed bladder trabeculation.

E.H., a 38-year-old female, presented with a one-year history of urinary incontinence. She had marked nocturia, frequency and urgency; her incontinence was primarily of the urge type, although coughing sometimes precipitated urgency but not incontinence. She had no other symptoms referable to neurological disease. General examination was normal but neurological examination revealed a very brisk jaw jerk, positive palmo-mental reflex on the right side, symmetrically exaggerated limb reflexes with bilateral Hoffmann's reflexes, finger flexion reflexes and extensor plantar responses. Urodynamic tests showed gross instability (to 60 cmH_2O) at 100 ml capacity with slow filling.

Discussion

Detrusor instability as a result of gross neurological disease is well recognised. The search for the cause of so-called "idiopathic" detrusor instability has so far been fruitless. There are many clinicians who believe that a neurophysiological basis is most likely and that the end organ abnormality arises from disordered function of some part of the neuraxis, anywhere between the bladder wall and the cerebral cortex (neurological or psychological). The opponents of this view point to the dangers of these assumptions in such a diverse group of patients. Although isolated neurogenic bladder dysfunction is rare, in our experience it is a well recognised entity in a small group of patients with residual bladder dysfunction following an otherwise complete neurological recovery from transverse myelitis.

The neurological diseases which are known to cause detrusor instability are usually major and pyramidal tract signs are a prominent feature. Detrusor instability has not previously been described with isolated pyramidal tract disease, nor has urinary incontinence been a major feature of descriptions of individual syndromes of pyramidal disease.

The patients described here had no neurological symptoms but all had severe urinary problems. They all had definite evidence of pyramidal tract disease. This group of 9 patients may represent a link between "idiopathic" instability and patients with major neurological disease producing instability. They may support the theory that all detrusor instability represents some disorder of the nervous system.

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A Prospective Trial of Bladder Training as Treatment for Detrusor Instability

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Summary—Bladder training, without the additional use of drugs, has been used as treatment for detrusor instability. In a 3-month prospective trial, with historical controls, nearly half of the treated patients were either cured or improved. Bladder training is, therefore, a successful non-invasive technique devoid of complications and is recommended for the treatment of mild detrusor instability.

It has been recognised for many years that symptoms of frequency, nocturia, urge incontinence and enuresis may be of psychological origin (Mosso and Pellicani, 1882). It is now known that detrusor instability is the urological abnormality often responsible for these symptoms (Bates, 1971). Treatment of detrusor instability by pharmacological manipulation or by direct surgical intervention has disappointing results. Treatment by bladder training has been recommended by Jeffcoate and Francis (1966) and recently Frewen (1978) has reported an 80% cure rate in females using a combination of bladder training and drug therapy.

The purposes of the present study were:

(1) To provide an objective assessment of the results of a 3-month period of bladder training without the additional use of drugs, and
(2) To determine which patients, if any, were most likely to benefit from this treatment.

Patients and Method

The trial consisted of a consecutive series of patients who fulfilled the following criteria:

(1) Cystometrically proven detrusor instability.
(2) Outflow obstruction excluded by objective assessment.
(3) No clinical evidence of neuropathy.
(4) Normal urine examination, intravenous urography and cystoscopy.
(5) Drug therapy was either stopped before admission to the trial or remained constant throughout its duration.

Twenty-eight patients were admitted to the trial. Their age distribution shows the 2 peaks characteristic of detrusor instability (Fig. 1).

Initial pre-treatment assessment of symptoms was made by interview and by reference to a 48-h record, kept by the patient, of the time and volume of each voiding. There was often a discrepancy between these 2 methods of symptomatic assessment. The final figures were reached after discussion of any differences with the patient. The observations recorded were:

(1) Frequency—average number of hours between voidings.
(2) Nocturia—average number of times per night that the patient was woken by the necessity to void.
(3) Incontinence—(*a*) Number of episodes per

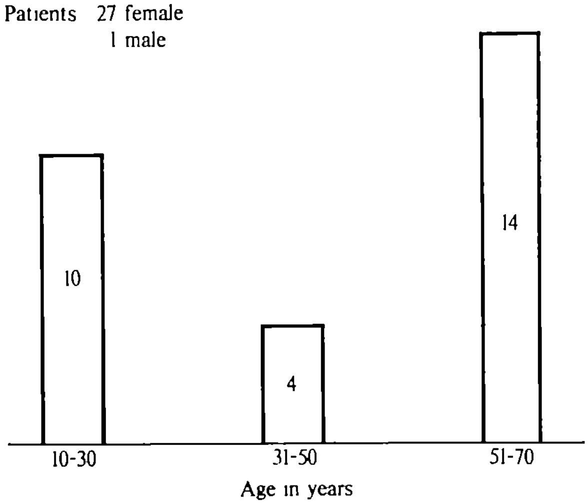

Fig. 1 Bladder training trial.

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> Passing of water is caused by contraction of the bladder. Normally the bladder does not contract until it is convenient to pass water, in other words the bladder contractions are under the control of the brain. In some unfortunate people this ability of the brain to control the bladder is lost. The bladder is then liable to contract at any time, even if its owner does not want it to. These uncontrolled bladder contractions are not in any way dangerous but are a common cause of frequency, urgency and leakage of urine.

Fig. 2 Uncontrolled bladder contractions.

day. (*b*) Number of changes of pads/pants per day.

(4) Nocturnal enuresis—number of wet beds per week.

Objective pre-treatment assessment was by the method of pressure-flow-videocystography developed at The Middlesex Hospital (Bates and Corney, 1971).

Treatment was as follows:

(1) The nature of detrusor instability was carefully explained. We felt that a clear understanding of the problem was so important that an explanatory leaflet was issued to every patient (Fig. 2).

> The aim of bladder training is to re-establish the brain's control over the bladder. Provided the exercises are performed with real determination the results are excellent and your urgency and leakage will be cured. Your own attitude of mind is one of the most important aspects of this treatment and we feel sure you will accept the challenge.
>
> You will be given a chart and a measuring jug. Every time you experience a desire to pass water you should write down the time in the first column. You must then try hard to regain control of your bladder by relaxing it, and holding on to your water. If you succeed, the desire to void will soon pass and you should put a cross in the "no leak" column. If leakage occurs before the desire to void passes off you should put a cross in the "leakage" column. If you are unable to hold on and have to pass your water you must measure the volume passed and write it down in the fourth column.
>
> Your must aim to:
>
> (*a*) abolish leakage,
> (*b*) hold your water for 4 h,
> (*c*) pass a volume of 400 cc.
>
> To begin with you will probably find you have to pass water fairly frequently and in small amounts, but provided you persevere you will soon see a great improvement. You will have to continue the exercises for about three months, by which time you should have regained control of your bladder and the improvement will be permanent.

Fig. 3 Bladder training exercises.

(2) The possibility of an emotional aetiology was discussed and a search was made for any emotionally disturbing event which might have occurred just prior to the onset of symptoms.

(3) Bladder training exercises were then explained and a second leaflet issued (Fig. 3) together with a chart for recording the time and volume of voidings and leakage. The patient was instructed to aim for 4 h between voidings, the abolition of leakage and never to void less than 400 ml at a time.

Follow-up, in out-patients, was at 2 and 6 weeks during which time micturition charts were kept.

Final assessment was made soon after 12 weeks of training exercises. The methods used at the initial assessment were repeated.

Controls were historical and selected from The Middlesex Hospital urodynamic clinic records. We had originally intended to have prospective controls but were unable to find a sufficient number of patients willing to wait 3 months without treatment before undergoing further videocystography. A list was therefore made from urodynamic records of all patients who had had more than one videocystogram. One of these was selected to match each of the trial patients for initial cystometry, sex, age and as far as possible, pre-treatment symptoms.

Results

Twenty-eight patients were admitted to the trial. One refused final videocystography and time and volume charts are not available on 2 others. Twenty-five patients, therefore, completed the protocol. Symptomatic changes for both trial and control patients are shown in Tables 1 and 2.

Name:
Date:

Time	*No leak*	*Leakage*	*Volume*

Fig. 4 Bladder training.

Table 1 Symptomatic Changes—Trial Patients

	Cured	*Improved*	*No change*	*Worse*
Frequency	13	8	4	
Nocturia	15	7	3	
Leakage	11	7	5	2
Overall assessment	7	12	5	1

Table 2 Symptomatic Changes—Controls

	Cured	*Improved*	*No change*	*Worse*
Frequency	2	5	16	2
Nocturia	5	4	15	1
Leakage	2	5	17	1
Overall assessment	1	7	16	1

Table 3 Cystometric Changes

	Cured	*Improved*	*No change*	*Worse*
Training	8	3	12	2
Controls	0	4	17	4

Nineteen of the trial patients were either improved or cured on overall symptomatic assessment; the corresponding number of control patients was 8.

Cystometric changes are shown in Table 3. The patient was not regarded as cured unless there had been a return to stable detrusor function. Improved cystometry was arbitrarily defined as a reduction by more than 25% in the height of unstable contractions or an increase of more than 25% in the bladder volume at which unstable contractions first occurred.

Eight of the treated patients returned to stable detrusor function; this did not occur in the control group.

Discussion

The results show that bladder training is an effective form of treatment in about half of the patients in this trial. In an attempt to identify patients most likely to benefit, the following pre-treatment factors were assessed: age, duration and nature of symptoms, type of cystometry (systolic contractions or a gradually rising cystometrogram), the strength of the unstable contractions, bladder capacity, initial in-patient or out-patient treatment. None of these factors was found to have any predictive value.

Three factors were associated with a poor result: (1) A history of nocturnal enuresis at any time after the age of 10 years (4 patients, all with a bad result). (2) A strong (above 100 cmH_2O) isometric contraction during voluntary interruption of micturition. This pressure was not available in all patients because complete interruption of flow was achieved in only 11 cases. (3) Failure to show an improvement within the first 2 weeks of treatment. There was not a single cured or improved patient who did not show an early response. There were, however, 2 patients who relapsed following an initially good response. It is likely that learning bladder control is similar to learning in other spheres; there is an initial steep rise in the "learning curve" followed by a plateau during which efforts must be maintained if relapse is to be avoided.

The study did not show any difference between in-patient and out-patient treatment but it seems sensible for patients to have a few days in hospital for initial intensive training during which the technique is learned. This should be followed by close out-patient supervision.

An emotionally disturbing event which might be regarded as the cause for detrusor instability was found in only 5 patients. Neither its presence nor absence was of prognostic significance.

The efficacy of past methods of treatment often seems to be related more to the enthusiasm of the doctors concerned than to the treatment itself. A possible explanation is that patients may inadvertently receive a form of bladder training while apparently undergoing different treatment. Many previous trials have included, in addition to the treatment under investigation, an explanation of detrusor instability together with the keeping of a micturition chart. These 2 procedures form the basis of bladder training.

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An Assessment of the Frewen Regime in the Treatment of Detrusor Dysfunction in Females

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Summary—Twenty-seven women with symptoms of frequency, urgency and urge incontinence were assessed urodynamically. Their detrusor behaviour fell into 3 groups: (1) reduced detrusor compliance, (2) uninhibited detrusor contractions, and (3) detrusor stability. Each patient was treated by Frewen's regime of bladder drill, detrusor inhibitory drugs, sedation and simple psychological counselling. At 3 months symptoms were markedly improved or cured in 86% of patients. Reduced compliance was the only detrusor abnormality which was reversible.

Detrusor dysfunction is responsible for symptoms of frequency, urgency and urge incontinence, and is one of the main areas in urological and gynaecological practice where treatment has been uniformly unsatisfactory.

The increasing use of urodynamic evaluation has demonstrated that detrusor abnormalities (particularly instability) are common, occurring in at least 30% of all patients presenting with urinary incontinence (Frewen, 1972; Torrens and Griffith, 1974).

Numerous forms of therapy have been evaluated. Surgical manoeuvres include partial bladder denervation (Ingelman-Sundberg, 1959) cystolysis (Worth and Turner-Warwick, 1973), bladder transection (Essenhigh and Yeates, 1973) and selective sacral neurectomy (Torrens and Griffith, 1974).

Several drugs have been investigated. These include propantheline Kieswetter and Popper, 1972), imipramine (Diokno *et al.*, 1972), flavoxate (Stanton, 1973), bromocriptine (Delaere *et al.*, 1978), emepronium bromide (Hebjørn and Walter, 1978), baclophen (Taylor and Bates, 1979), indomethacin (Cardozo and Stanton, 1980), flurbiprofen (Cardozo *et al.*, 1980) and oxybutinin (Diokno and Lapides, 1972).

Some success has been reported using prolonged bladder distension (Ramsden *et al.*, 1976), but Pengelly and associates (1978) using a similar method have reported poor results. Early results using biofeedback have been promising, although the technique is extremely time-consuming (Cardozo *et al.*, 1978).

Frewen (1972) suggested that idiopathic bladder instability in females is of psychosomatic origin. He provided evidence of objective remission in over 80% of cases using a combination of bladder drill, detrusor inhibitory drugs, sedation and simple psychological counselling (Frewen, 1978). In most patients he was able to find an emotional precipitating factor which could be related to the onset of symptoms.

Support for a psychosomatic aetiology was provided by Hafner and associates (1977) who demonstrated a strong correlation between psychological disorder and symptoms of frequency, urgency and urge incontinence.

This study evaluated the effectiveness of the Frewen regime in a group of women with these symptoms.

Patients and Method

Twenty-seven female patients with symptoms of increased frequency, urgency and urge incontinence were studied. Six patients were excluded (Table 1). Thus 21 patients completed the study and were followed up for an average of 12 months (range 4-18 months). Their average age was 45.8 years (range 12-69 years).

Table 1 Reasons for Failure to Complete Study

Failure to continue medication at home	2
Severe side effects	2
Self discharge from hospital	1
Refused follow-up urodynamic study	1

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Each patient was assessed by videocystometry. Three patients had normal urodynamics. Eleven patients showed a steep pressure rise on filling to greater than 15 cm of water and were considered to have reduced detrusor compliance. Seven patients demonstrated uninhibited contractions on filling or provocative testing.

Neurological abnormalities, diabetes mellitus, outflow obstruction, urine infection and organic bladder pathology were excluded by appropriate physical examination, urine testing, uroflowmetry, bacteriological examination and cystoscopy. Increased frequency was defined as voiding more often than 2-hourly during the day or more than once at night. Patients were questioned in an attempt to define a precipitating emotional factor relating to the onset of symptoms. Most patients were admitted to hospital for their initial therapy, but 3 were treated as out-patients. They were all prescribed Cetiprin (emepronium bromide) 200 mg tds and 400 mg *nocte*, together with Motival (nortryptyline and fluphenazine) one tablet tds.

A micturition chart was given to each patient with instructions to record each time they urinated, the quantity of urine passed and whether or not incontinence occurred. They were instructed to resist the urge to void for as long as possible, even at the risk of precipitating incontinence. Emphasis was placed on the importance of retraining the bladder so as to encourage cortical control, rather than allowing unstable detrusor contractions to dictate the voiding frequency.

Patients remained in hospital for up to 10 days. After discharge they were seen monthly. Outpatients were seen weekly for the first month. After 3 months a further urodynamic study was performed. Drug therapy was continued throughout this period.

Results

Urge incontinence was the most troublesome symptom and has been used as a baseline in assessing response to treatment. An improvement in urge incontinence implied a reduction in leakage to once a day or less. Thus 7 out of 21 patients (33%) were improved and 11 out of 21 patients (52%) were cured of this symptom, an overall response rate of 86% (Table 2).

Table 2 Effect of Treatment on Symptomatology (N = 21)

	No change	*Improved*	*Cured*
Frequency—diurnal	5	4	12
—nocturnal	5	1	15
Urgency	3	8	10
Urge incontinence	3	7	11
Stress incontinence	1	—	4
Enuresis	—	—	2

Table 3 Correlation of Urodynamic and Symptomatic Results

Detrusor behaviour				*Symptoms*	
Before		After			
Stable	3	Stable	3	Cured	2
				Improved	1
Reduced compliance	11	Stable	5	Cured	5
		Unchanged	6	Cured	2
				Improved	3
				Unchanged	1
Systolic	7	Unchanged	7	Cured	3
				Improved	2
				Unchanged	2

Patients were then assessed according to their detrusor behaviour and comparison made between urodynamic and symptomatic results (Table 3).

Two of the 3 patients with stable bladders were cured of their symptoms.

In the patients with reduced compliance, 5 of the 11 became stable (Fig. 1) and all were symptomatically cured. The remainder were unchanged urodynamically and although 2 of these were symptomatically cured, they both relapsed when their drug therapy was stopped. These 2 patients required a further course of bladder drill and long-term drug therapy to maintain relief of their symptoms, as did one patient in the improved group.

There was no objective improvement in those patients in whom uninhibited contractions were elicited, despite the fact that 3 were symptomatically cured. The 2 patients in this group who were improved are both maintained on drugs.

Altogether 5 of the 21 patients continued to need drug therapy, all of whom demonstrated no significant urodynamic improvement.

A probable precipitating factor was discovered in 9 of the 27 patients (Table 4). There was no correlation between the results of treatment and the definition or otherwise of this factor.

Significant side effects were few (Table 5) but dryness of the mouth proved troublesome. Two patients were withdrawn because of oesophagitis. This complication was presumably related to the

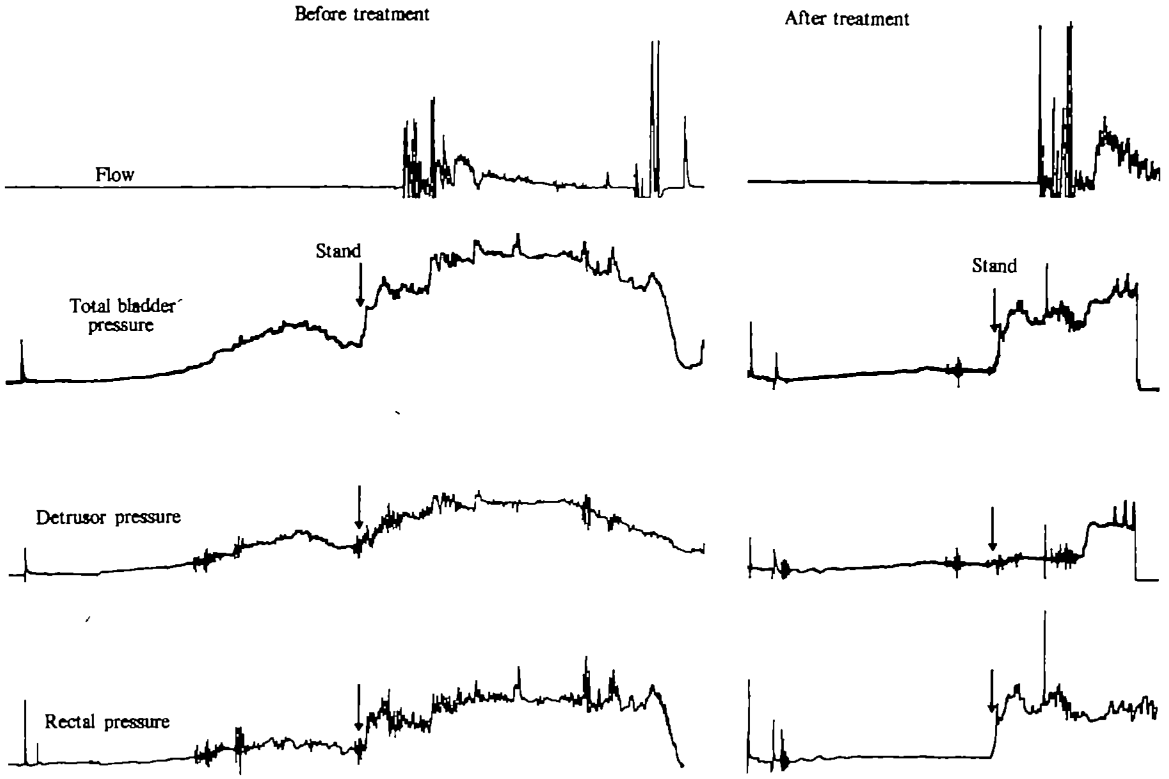

Fig. 1 Urodynamic findings before and after bladder training

effect of the anticholinergic drugs on the gastro-oesophageal sphincter.

A hospital stay of up to 10 days, although enforced in most patients, was probably unnecessary. Equally good results were obtained in 3 patients treated entirely on an out-patient basis.

Discussion

The large number of treatments evaluated in idiopathic detrusor instability implies the failure of any one regime to produce an acceptable cure rate. Frewen (1978, 1980) has reported more success than most using a combination of anticholinergic drugs, sedation, bladder drill and simple psychological counselling.

This study was designed to evaluate further the effectiveness of the Frewen regime. Our results indicate that patients with the symptom complex of frequency, urgency and urge incontinence may be urodynamically normal, may have reduced detrusor compliance, or may exhibit uninhibited detrusor contractions. Symptomatic cure or marked improvement occurred in 86% of patients. Reversion to stability was recorded in only 28% and was confined to those patients with reduced detrusor compliance who were symptomatically cured.

There are several well recognised causes of the frequency, urgency and urge incontinence syndrome which tend to be grouped together under the heading of the urethral syndrome (Fig. 2).

Table 4 Factors Relating to Onset of Symptoms

Hysterectomy	3
Conversion from childhood eneuresis	2
Vaginal repair	1
Hospital admission	1
Marital dysharmony	1
Parturition	1

Table 5 Side Effects from Drugs

Dry mouth	10
Oesophagitis	2
Perioral twitching	1
Lethargy	3

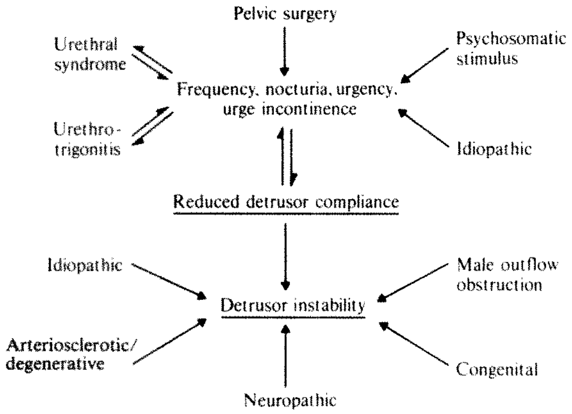

Fig. 2 A concept of detrusor behaviour.

In patients with stable bladders it seems likely that those with hypersensitivity and those with recurrent urinary infection may fare less well than those who develop symptoms following pelvic surgery, or for no obvious cause.

In concept, the majority of patients with detrusor dysfunction may have stable bladders initially, and it may be the frequent micturition itself which causes the compliance of the bladder to be reduced. This frequency may also induce the squamous change in the bladder base which is generally termed urethrotrigonitis.

In some patients, reduced detrusor compliance may progress to uninhibited contractions which, although apparently irreversible, may still respond symptomatically to bladder training, although it remains to be seen whether this response is permanent.

It would seem illogical from a diagnostic or treatment point of view to differentiate between those patients with a steep cystometrogram and those with the same symptom complex and a stable bladder. Greater numbers in all groups are needed to clarify the situation. There is no doubt, however, that reduced compliance in our hands is the one detrusor abnormality which is reversible.

Those patients with arteriosclerotic or neuropathic bladders with high pressure uninhibited contractions are clearly not suitable for the treatment and are unlikely to respond.

Self help is the mainstay of the Frewen regime and it is noteworthy that biofeedback, which also involves this principle, is the only other treatment which has produced a comparable success rate. The advantage of the Frewen treatment is its simplicity.

In summary, the Frewen regime will provide a marked improvement or cure in the majority of patients with symptoms of frequency, urgency and urge incontinence. A return to urodynamic normality will be likely to occur only in those patients with low compliance bladders who are symptomatically cured.

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The Urodynamic and Subjective Results of Treatment of Detrusor Instability with Oxybutynin Chloride

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Summary—The results of a double-blind controlled trial using oxybutynin chloride in 30 patients are described. Twenty-three patients completed the study; 17 of these had symptomatic improvement and 9 patients had urodynamic improvement. Seventeen patients had significant side effects.

The variety of treatment regimes for detrusor instability used over the years is an indication of the problems involved in obtaining a satisfactory response and also indicates the lack of understanding of the precise pathological processes involved. Numerous drugs, either alone or in combination, have been used with additional bladder re-training techniques. Prolonged bladder distension has given satisfactory results in some centres (Dunn *et al.*, 1974; Ramsden *et al.*, 1976), but others have been unable to match these results (Pengelly *et al.*, 1978). More invasive techniques including cystolysis (Worth and Turner-Warwick, 1973) or selective sacral neurectomy (Clarke *et al.*, 1979) are unpredictable and should be reserved for special cases.

Oxybutynin chloride exerts a dual action—an anticholinergic effect and a direct spasmolytic effect on the bladder smooth muscle. Patients receiving treatment have reduced urgency, urge incontinence and micturition frequency. Improvements can also be demonstrated on urodynamic studies with an increase in the bladder volume before unstable contractions occur, an increase in total bladder capacity and the reduction in the frequency and intensity of abnormal detrusor contractions. Previous reports, in patients with neurological disease, describe symptomatic improvements in up to 75% compared with a placebo improvement of 25% (Diokno and Lapides, 1972).

The results of a randomised double-blind controlled trial in 30 unselected patients using oxybutynin chloride 5 mg tds and a placebo are presented.

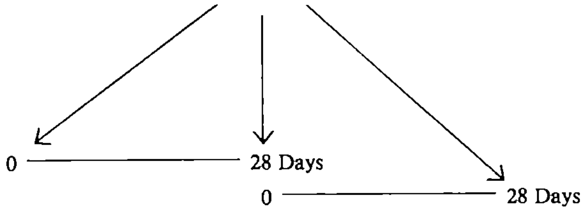
Patients and Methods

Thirty patients with proven detrusor instability, as defined by the Standards Committee of the International Continence Society, entered the trial. The patients included newly diagnosed cases and a number who had failed to respond to previous drug therapy or bladder re-training.

Seven patients withdrew from the trial because of severe side effects in 5, pregnancy in 1 and viral illness in 1. Twenty-three patients completed the study. There were 10 male and 13 female patients, ages ranging from 20 years to 79 years. The cause of detrusor instability was idiopathic in 12 patients, post-obstructive following prostatectomy in 4 patients, and neurogenic in 7 patients, due to multiple sclerosis, cerebrovascular accident and spina bifida.

An initial general medical history and examination was made. A full urological history was recorded on a standard pro forma and repeated at each subsequent visit and any side effects were noted. Urodynamic studies were performed im-

Table 1 Urodynamics and Subjective Assessment



	Course 1	*Course 2*
Oxybutynin	12	11
Placebo	11	12

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 "Idiopathic" Group: Effect on Symptoms: Oxybutynin Chloride

	Diurnal frequency (9)	*Nocturia (9)*	*Urgency (7)*	*Urge incontinence (4)*
Unchanged	2	3	1	0
Improved	4	3	2	1
Normal	3	3 nil	4 absent	3 dry

Only 2 patients had all symptoms relieved.

mediately prior to entering the trial and during the last day of each treatment course. Patients, who were randomly allocated, received consecutive 28-day courses of placebo, or oxybutynin chloride 5 mgm tds, both identical in appearance (Table 1).

Results

Seventeen (69%) of the 23 patients who completed the trial had symptomatic improvement; 9 patients had improvement on urodynamic assessment. The results of the 3 categories of patients are described separately in more detail.

Idiopathic Group—12 Patients

Nine of these patients had subjective improvements during treatment with oxybutynin chloride, whereas only 1 patient improved with the placebo. This exceptional patient converted from severe detrusor instability to stability following his betrothal. The remaining 3 patients were not improved.

Diurnal frequency was reduced in 7 out of 9 patients, nocturia in 9 patients became absent in 3, and was improved in a further 3 patients. Six out of 7 patients had reduced urgency of micturition and all 4 patients with urgency incontinence were improved. Only 2 patients had all their symptoms relieved (Table 2).

Urodynamic improvements were demonstrated in 5 out of the 9 patients, 2 patients converting to detrusor stability. Four patients who were subjectively improved had unchanged urodynamic studies. The main urodynamic changes were increase in bladder volumes at first detrusor contraction and in total bladder capacity (Table 3).

Post-obstructive Group—4 Patients

Three patients had subjective improvement on oxybutynin chloride and 1 patient was improved by the placebo. The main subjective change was loss of urgency of micturition in all patients who were improved. Other symptoms improved included reduced nocturnal incontinence, nocturia, and diurnal frequency. Urodynamic studies, however, showed improvement in only 2 patients, 1 of whom became stable whilst on the active drug (Table 4).

Neurogenic Group—7 Patients

Five patients noticed subjective improvement. There was no response to the placebo in any patient. The most significant change was in 3 patients, who developed full urinary control at night. Other symptoms that improved included reduction in diurnal frequency in 2 patients and less nocturia in 1 patient. Two patients had

Table 3 "Idiopathic" Group: Urodynamic Results: Symptomatically Improved Patients

Bladder volume at onset instability (ml)		*Change*	*Bladder capacity (ml)*		*Change*	*Detrusor pressure at capacity (cm) water*	
Initial	*Oxybutynin*		*Initial*	*Oxybutynin*		*Initial*	*Oxybutynin*
50	200	+150	150	275	+125	25	20
500	500	—	500	500	—	40	15
400	600	+200	400	600	+200	60	15
400	550	+150	600	600	—	70	70
300	550	+250	500	600	+100	25	20
400*	400	—	400	400	—	25	20
425*	350	−70	425	350	−70	30	20
350*	350	—	400	400	—	20	25
100*	100	—	660	675	+15	25	35

* No urodynamic improvement.

Table 4 Post-obstructive Group: Urodynamic Results: Symptomatically Improved Patients

Bladder volume at onset instability (ml)		*Change*	*Bladder capacity (ml)*		*Change*	*Detrusor pressure at capacity (cm) water*	
Initial	*Oxybutynin*		*Initial*	*Oxybutynin*		*Initial*	*Oxybutynin*
350	Stable	—	350	370	+20	30	12
250	350	+100	275	450	+175	50	25
240*	250	+10	350	300	−50	30	20

* No urodynamic improvement.

improvements in their urodynamic measurements in spite of the permanent nature of their neurological disorder (Table 5).

Side Effects

Seventeen out of the 30 patients entering the trial had side effects (Table 6). Several of the symptoms noted may not have been directly attributable to oxybutynin chloride. The main problem in 13 patients was dryness of the mouth. Five patients were unable to finish the 28-day course, mostly because of the oral effects. Of these, 3 patients considered their urinary symptoms improved but the side effects intolerable. Other patients thought the urinary symptomatic improvement far outweighed the disadvantage of dryness of the mouth.

Discussion

A number of trials of drug treatment for patients with detrusor instability have produced varied and unpredictable results, often with a high incidence of side effects. In several series there has also been the marked placebo effect; this is especially noticeable in uncontrolled trials. The present trial was designed to reduce the placebo effect by using a double-blind controlled technique. However, patients or the observer may have been aware that the active drug was being taken due to the occurrence of side effects.

A comparison of flavoxate, emepronium chloride and propantheline (Gaudenz and Weil, 1978) showed an overall subjective improvement in 83% of patients taking flavoxate. The other 2 drugs were less effective: emepronium bromide had 66% improvement and propantheline 43% improvement. However, in this series some subjective improvement was noted in 78% of the patients taking placebo.

Bromocriptine has not stood the test of time and in a recent study was no better than placebo (Abrams and Dunn, 1979) with 50% improvement in both groups. Other drugs studies included indomethacin (Cardozo and Stanton, 1978) and flurbiprofen but these were in female patients with idiopathic detrusor instability. Flurbiprofen was especially helpful in reducing severe urgency and enuresis. Indomethacin was less effective but did improve diurnal frequency and nocturia. However, the occurrence of side effects was very high.

In a study of 40 patients with unstable bladder syndrome taking baclofen (Taylor and Bates, 1979), 52% of the patients considered themselves improved on baclofen and 40% on placebo. However, the patients were not assessed urodynamically.

The most impressive results to date have been by Frewen (1978), who reported an 82% cure rate in 40 patients with idiopathic detrusor instability. However, other workers have failed to approach their excellent figures.

Table 5 Neurogenic Group: Urodynamic Results: Symptomatically Improved Patients

Bladder volume at onset instability (ml)		*Change*	*Bladder capacity (ml)*		*Change*	*Detrusor pressure at capacity (cm) water*	
Initial	*Oxybutynin*		*Initial*	*Oxybutynin*		*Initial*	*Oxybutynin*
350	550	+200	350	550	+200	60	45
450	600	+150	600	650	+50	45	20
400*	400	—	550	450	−100	45	40
125*	125	—	150	150	—	55	55
50*	50	—	100	150	+50	30	40

* No urodynamic improvement.

Table 6 Side Effects

Dry mouth	13
Ocular	1
Drowsiness	3
Headaches	1
Dizziness	1
M S. worse	1
Ankle swelling	1

The patients studied in this series were a difficult mixed group, including patients with established and often advanced neurological disease and other patients who had failed to respond to other routine treatment regimes. Therefore the 69% rate of symptomatic improvement is a very convincing figure compared with the 8% improvement on placebo.

Symptomatic improvement occurred within the first few days of taking the drug and therefore patients who fail to respond early would not benefit from a prolonged course of therapy. The reduction of symptoms such as urgency and urgency incontinence is especially beneficial to these patients even though there may not be total symptom relief. The high incidence of side effects poses a real problem, as with many other drugs, but most patients tolerated them and in those completing the 28-day course the side effects became less noticeable as time went on.

The assessment of urodynamic changes is more difficult as in most patients these did not match the symptomatic improvement. Three patients converted to stability and variable, though significant, changes occurred in the remaining 6 patients. The occurrence of these real urodynamic improvements is a further indication of the usefulness of oxybutynin chloride. Few of the other drugs previously studied have demonstrated both symptomatic and urodynamic improvements comparable with the results in this series.

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Eskornade in the Treatment of Diurnal Incontinence in Children

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Summary—This study examined 75 children with daytime wetting and particularly those with some form of bladder neck incompetence. There was a good response in 75% of cases to Eskornade (containing phenylpropanolamine, an α adrenergic agonist), but a lesser response in children with bladder instability. Large doses of this preparation have sometimes been necessary to produce urinary continence and side effects, although common, were usually minor and transient.

Urinary incontinence is a common and distressing symptom in children and although nocturnal enuresis is the most frequent urinary complaint in children referred to the urologist, diurnal incontinence is more disruptive socially and psychologically to child and parent alike.

The role of the autonomic nervous system in the control of bladder function has been known for more than half a century. Tanagho and Meyers (1969) used sympathomimetic substances to increase proximal urethral resistance. Kleeman (1970) and Krane and Olsson (1973) used α adrenergic blockade to reduce outlet resistance and improve bladder emptying. Lapides reported in 1974 on his use of ephedrine in various groups of patients with incontinence. Phenylpropanolamine (an α adrenergic agonist) has been used to treat diabetics with retrograde ejaculation by Stewart and Bergant (1974) and in 1976 Stewart *et al.* were encouraged by the use of the same drug in women with stress incontinence, but disappointed with its effect in post-prostatectomy incontinence.

This study records experience in the use of an α adrenergic agonist in the treatment of children with daytime wetting from a variety of causes by promoting bladder neck closure and possibly in addition by stimulating the distal mechanism (Fig.).

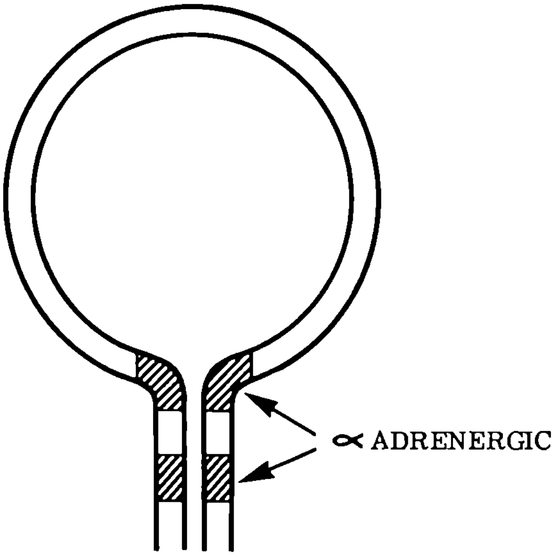

Fig. Sites of action of α adrenergic agonists on urinary continence mechanism.

Patients and Methods

Eighty-three children between the ages of 5 and 19 (mean age 9 years) have been treated as outpatients with Eskornade (Smith, Kline and French Laboratories Ltd). This preparation is presented as a sustained release capsule containing phenylpropanolamine 50 mg (α adrenergic agonist), Isopropamide 2.5 mg and diphenylpyraline 5.0 mg (both antihistamines with anticholinergic properties). Eskornade can also be obtained in syrup form (20 ml is equivalent to one capsule), and has been used for 20 years as a nasal decongestant in the treatment of hay fever and allied conditions.

Seventy-two of the children attending clinics at the Hospital for Sick Children, Great Ormond

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Primary Diagnosis

	Stable	*Unstable*
Bladder neck incompetence	42	18
Others		
Neuropathic	8	8
Other unstable	3	3
Giggle incontinence	3	2
Small bladder	2	
Cause undetermined	6	

Street and the Shaftesbury Hospital had daytime wetness ranging from "giggle incontinence" to continuous and complete incontinence. Fifty-two of these were also wet at night. Eight have not been followed up for more than 3 months and are not included in the analysis. Five children with anal incontinence following ureterosigmoidostomies and six children with simple nocturnal enuresis have also been treated and are considered as separate groups. Altogether 40 girls and 35 boys with adequate follow-up have been thoroughly assessed urologically. Urodynamic studies were considered not to be justified in many of the younger children but were performed in most of those over 8 years old.

The children with diurnal incontinence were placed in various diagnostic categories (Tables 1 and 2). Forty-two (65.6%) were defined as having incompetent bladder necks. Eighteen of these had unstable or high pressure bladders in whom the bladder neck dysfunction may not have been the primary problem.

Sixty-three per cent had been treated unsuccessfully with drugs including imipramine, amitriptyline, propantheline, emepronium and flavoxate. Many of the cases were the hard core of incontinent children who had failed to respond to any medication.

Treatment with Eskornade was usually started with one capsule 12-hourly or 10 ml of syrup 8-hourly and increased gradually until urinary continence was achieved or side effects appeared.

Table 2 Bladder Neck Incompetence

	Stable	*Unstable*
Epispadias	8	
Rectal agenesis	7	5
Other neuropathic	7	7
Valves	3	
Reconstructed exstrophy	3	
Others	14	6

Table 3 At Follow-Up

	n *24*	*n* *31*	*n* *75*
	Bladder neck incompetence (%)	*Bladder instability (%)*	*Overall (%)*
Cured	41	24	35
Minimal symptoms	29	24	26
Improved	12	20	14
Minimal improvement Same	16	28	22
Worse	2	4	3

A maximum of 2 capsules 8-hourly was used in the older children. This is 3 times the recommended adult dose, but this high dosage was necessary in some cases to produce continence. Adverse reactions and side effects are considered later.

Results (Table 3)

"Cured" means completely dry day and night. "Improved" includes those who continued to have some wet episodes but the children and/or parents considered the treatment to have been worthwhile. Overall, 75% of the 75 children treated and adequately followed up were classified as responders (cured + minimal symptoms + improved). Of those with identifiable bladder neck incompetence the response was a little better, at 82%.

Of those children with uncomplicated bladder neck incompetence 42% were cured compared with only 24% of children with bladder instability.

Nineteen children were non-responders (minor improvement + same + worse) and of these there seemed to be good reasons for failure in 9 (inadequate dose in 4, non-compliance in 3, severe side effects in one, and one girl had an ectopic ureter bypassing the continence mechanism.

Several groups of patients were analysed separately:

(a) Ureterosigmoidostomy

There were 5 cases with anal incontinence. Three developed complete control, one was greatly improved and the fifth, although cured of his incontinence, became so aggressive that Eskornade had to be withdrawn.

(b) Giggle Incontinence

Two were cured and remained symptom-free on treatment, while the third took a prophylactic capsule when she anticipated a "giggle" situation such as a party and has remained dry.

(c) Nocturnal Enuresis

Five children with simple enuresis have been treated with Eskornade. Three of these became completely dry, one wets very rarely and the fifth has shown no response.

(d) Intermittent Self-catheterisation

Three of the children with neuropathic bladders were wet between catheterisations and this form of treatment might have been abandoned but for the response to Eskornade; one became completely dry and the other 2 had only rare accidents or minor dampness on treatment.

(e) Children who Avoided Major Surgery

Four children avoided major surgery. One exstrophy closure who was seriously considered for a second bladder neck reconstruction (or diversion for failure) now has almost complete control on Eskornade. One incontinent girl became asymptomatic and her proposed bladder neck reconstruction has been cancelled. Another boy (16 years old, posterior urethral valves resected as an infant) was considered for implantation of a continence device when puberty did not bring about the expected improvement. He is virtually dry on Eskornade. Lastly, a 19-year-old girl with sacral agenesis and a neuropathic bladder (one of those using intermittent self-catheterisation) is now very rarely damp on treatment. Bladder denervation had been planned.

Side Effects

Treatment was withdrawn in 8 children because of side effects. Six of these had shown a response in spite of side effects and the improvement was maintained after the drug had been discontinued. Two were cured, 3 have minimal symptoms and one is improved. One of the non-responders developed severe nose bleeds in addition to nasal and oral dryness. Hypertension has been recorded as a side effect of Eskornade used in adults but was not seen in this series of children. This was not a routine measurement in the current study but was recorded regularly in those children (37) with potential or established upper tract disease. No deterioration in renal function has been recorded in any child on treatment.

There were 23 children with mild and transient side effects (Table 4). The unwanted symptoms either resolved spontaneously while continuing the medication or disappeared by reducing the dose of Eskornade.

The drug was gradually withdrawn in 18 children following treatment for between 2 and 9 months. Ten of the 18 have relapsed and Eskornade was recommenced. In response to this second course of treatment 6 have become either asymptomatic or have minimal symptoms once more; one has failed to respond and 3 have not yet been followed up.

Discussion

This was not a controlled trial but a retrospective analysis of the effect of Eskornade on children with diurnal incontinence. Undoubtedly there was a certain amount of patient selection, in that some were included specifically because of a suspicion or confirmation of bladder neck dysfunction, in the knowledge that an α adrenergic stimulator might be an appropriate form of treatment.

Eskornade is a compound drug and its anticholinergic component may contribute to its success by relaxing the detrusor muscle. However, the significantly worse response in children with bladder instability suggests that the α adrenergic activity of phenylpropanolamine is the most significant factor. However, many of the patients with either bladder instability or overtly neuropathic bladders also did well.

The parents of those patients who responded often described the effects of the drug in glowing terms. Phrases such as "wonder drug", "miracle", "marvellous" were frequently expressed and the fact that 4 children have avoided major surgery in this series has given equal satisfaction.

Table 4 Side Effects

		Treatment stopped
Drowsiness	14	2
Dry mouth/nasal passages	7	2
Behaviour disturbance	5	3
Blurred vision	2	
Chest tightness	2	
Abdominal pain	1	1

There has been concern about the large doses of Eskornade necessary to produce the desired therapeutic effect in some of the children. However, although side effects were common they were easily tolerated by most, because of the often dramatic improvement in continence. In those in whom side effects were sufficiently severe to terminate treatment, no permanent sequelae have been observed.

Eskornade also has an effect on the anal sphincter as well as the bladder neck, as suggested by the improved continence in children with ureterosigmoidostomies.

The apparent success of Eskornade in this study suggests the need for a controlled prospective trial to confirm its effectiveness. Such a trial to compare Eskornade *v*. phenylpropanolamine *v*. placebo is in preparation.

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Bladder Transection for Urge Incontinence Associated with Detrusor Instability

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Summary—Twenty-three adults with incapacitating urge incontinence associated with urodynamically proven detrusor instability were treated by bladder transection after conventional non-operative treatment had failed. The operative technique is described. Subjective normality was restored in 78% of patients and objective evidence of improvement is documented.

The concept of bladder transection was introduced by Turner-Warwick and Ashken in 1967 although they described the procedure as a cystocystoplasty. Yeates (1970) described a modification of this procedure and the Newcastle and Liverpool groups have presented preliminary and extended series, using this modified technique in a total of 80 patients with primary enuresis, the enuretic syndrome and urge incontinence (Essenhigh and Yeates, 1973; Gibbon *et al.*, 1973; Hindmarsh *et al.*, 1977; Parsons *et al.*, 1977). Janknegt *et al.* (1979) reported a further 10 patients with enuresis who had transections. The operation was worthwhile in about 75% of these 90 patients. However, despite the disillusionment with Helmstein distension in patients of this type who fail to respond to chemotherapy with anticholinergic drugs (Pengelly *et al.*, 1978), bladder transection does not seem to have found a wider acceptance, possibly because the operation has been reported as being ill-conceived when symptoms are associated with urodynamically proven detrusor instability (Turner-Warwick, 1979). This report presents the results of bladder transection in 23 patients with urge incontinence associated with detrusor instability.

Patients and Methods

There were 23 patients, 22 female and 1 male, with a mean age of 43.6 years (range 19-79). Symptoms had been present for a mean of 21.7 years (range 4-53) and no satisfactory response had been achieved from previous treatment with pharmacological agents (all patients) or Helmstein procedures (15 patients). Twelve of the females had had previous unsuccessful surgery for stress incontinence. In all instances symptoms were such that the patients were willing to accept what was described to them as an experimental procedure.

Table 1 lists the symptoms in these patients with urgency and urge incontinence and/or bedwetting as the common denominators. Two patients voided 2-hourly by day, the other 21 voided once an hour or more with a mean of 27.7 min between voidings. Fifteen patients had nocturia with a mean frequency of 5.2 times a night. The pre-operative urodynamic findings are listed in Table 2 and showed spontaneous detrusor instability in 6 patients and instability induced by provocation in 17 patients. In all patients the upper urinary tract was normal on intravenous urography.

Operative Technique

The technique used was a modification of that previously described by Essenhigh and Yeates

Table 1 Symptoms

Frequency (mean)	21 patients	27.7 min	
Nocturia (mean)	15 patients	5.2 times a night	
Urgency	23 patients	<5 min postponement	13
		5-10 min postponement	9
		10-15 min postponement	1
Urge incontinence	19 patients	Several times a day, every day	2
		Every day	9
		Several times a week	8
Bed wetting	11 patients	Every night	4
		Several nights a week	7

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Urodynamic Findings

"Systolic" pattern during supine filling	6
Unstable contractions induced by coughing	5
Unstable contractions induced by postural change	7
Unstable contractions induced by coughing and by postural change	5

(1973). The bladder was exposed through a Pfannenstiel incision and freed from the anterior and lateral pelvic walls by blunt dissection. The dome of the bladder was then opened by a vertical cystotomy and the ureters intubated with 5 FG or 8 FG infant feeding tubes. The transection was started posteriorly just above the interureteric bar to establish the extravesical plane anterior to the vagina or the rectum and seminal vesicles. As the transection was extended laterally above the ureteric orifice a second plane of tissue was found between the bladder wall and the ureter, comprising neurovascular elements in the perivesical connective tissue (Fig. 1). This was divided with the bladder wall. It was to define this perivesical tissue clearly that the transection was started posteriorly. Once the transection had been extended to the lateral wall of the bladder and could be clearly seen from outside the bladder (Fig. 2), a second transverse incision was made through the bladder wall in the anterior midline 1 cm above the internal meatus. This incision was then extended posterolaterally to join the posterior incision, again transecting both the bladder and the perivesical tissue (Fig. 3). After achieving haemostasis in the perivesical tissue, that side of the bladder was then reconstituted with one layer of continuous chromic catgut. The other side of the bladder was transected and reconstituted in the same way and the vertical cystotomy was closed over a suprapubic catheter. An extravesical wound drain was placed before wound closure. In every case but one, wound drainage ceased in 2 to 3 days and the drain was then removed. The suprapubic catheter was clamped on the seventh day and removed 24 h later. These 22 patients left hospital on the ninth or tenth post-operative day.

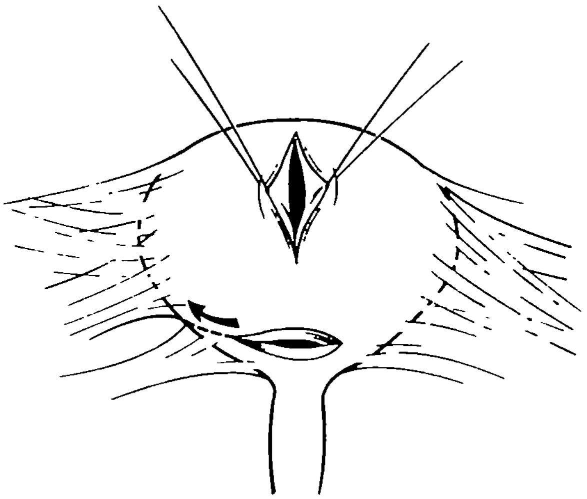

Fig. 2 Operative technique 2. Anterior transection incision extended posterolaterally from outside the bladder to include the perivesical tissue and join the posterior transection.

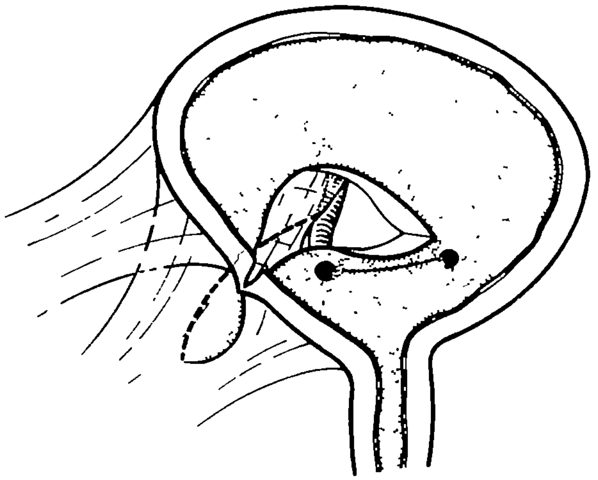

Fig. 1 Operative technique 1. The perivesical tissue is seen (and divided) between the bladder wall and ureter as the posterior incision is extended laterally.

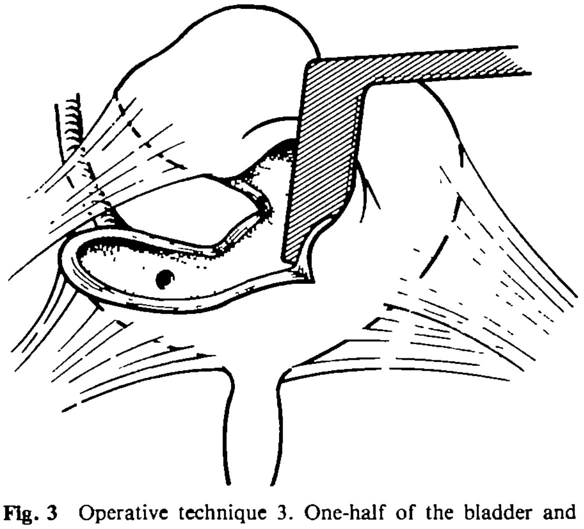

Fig. 3 Operative technique 3. One-half of the bladder and perivesical tissue transected.

Table 3 Results of Bladder Transection

		Follow-up 13.7 months (8-25 months)		
Excellent	9	Asymptomatic	7	78%
		Nocturia × 1	2	
Very good	11	"Urgency" (*c.* 30 min postponement)	5	
		"Urgency" (*c.* 30 min postponement) + Nocturia × 1	4	
		Occasional bed wetting	2	
Good	2	F = 4/h → ½ h; N × 10 → N × 1; mild incontinence	1	
		F = 3/h → ½ h; N × 4 → N × 0; mild incontinence	1	
Failure	1	No improvement		

Results

One patient had a persistent urinary leak from the bladder which required reoperation. Two patients developed post-operative wound infections which resolved spontaneously and one patient (aged 71) developed a chest infection which resolved on antibiotics. One patient developed infected urine before her discharge from hospital and 4 others developed urinary infections at home during the first 3 months. No other complications were seen.

All patients have been followed up for a mean of 13.7 months (range 8-25). The results of operation are shown in Table 3. One patient was a failure, with no improvement at all. The remainder were all pleased with the result of the procedure. Two patients had some residual slight incontinence, requiring them to change their underwear once during the day. Nine patients were either asymptomatic or had nocturia × 1 but of the 2 with nocturia, one was 79 years old and the other felt that he woke from habit. Eleven are classified as very good results: 2 of them have wet their beds 2 or 3 times since operation but are asymptomatic by day. Nine patients still have some sensation of urgency but the sensation is far less and postponement for up to half-an-hour can be regularly achieved; these patients could thus be regarded as normal (except under the strictest criteria) giving an overall subjective cure rate of 78% (18 patients). Table 4 compares the pre-operative and post-operative subjective evaluations.

Objective evaluation was achieved in the first 9 patients by urodynamic studies. Of these, 3 were normal and 6 showed a "shift to the right" (Gibbon *et al.*, 1973). As the most important

Table 4 Comparison of Subjective Findings Before and After Bladder Transection

Symptom		*Pre-operative*	*Post-operative*
Frequency (mean)		35.7 min (15-120)	161.7 min (60-240)
Nocturia (mean)		5.2 times (n = 15)	1.5 times (n = 6)
Urgency	5 min	13 patients	1 patient
	5-10 min	9 patients	—
	10-15 min	1 patient	—
	15-30 min	—	9 patients
Urge incontinence	*	2 patients	1 patient
	†	9 patients	—
	‡	8 patients	—
	§	—	—
	¶	—	2 patients
Bed wetting	†	4 patients	—
	‡	7 patients	—
	§	—	—
	¶	—	3 patients

* Several times a day, every day.

† Every day.

‡ Several times a week.

§ Once a week.

¶ Occasional.

parameter of success appeared to be improved bladder capacity, subsequent patients have been assessed by mean voided volume over a 24-h period. This has shown an improvement in these 14 patients (including the failure) from a mean of 80.6 ml±18.6 SEM to a mean of 326.4 ml±15.3 SEM.

Discussion

Although chemotherapy for urge incontinence associated with detrusor instability would be preferable to surgery, currently available drugs have produced disappointing results (Milroy, 1979). The bladder retraining programme advocated by Frewen (1978) looks very promising but is unlikely to achieve universal success. Thus it seems likely that there will always be a group of patients for whom a surgical procedure may be the only escape from either continued incontinence, with its emotional and social implications, or permanent indwelling catheterisation or enterocystoplasty or even urinary diversion. The findings of this report would support previous studies in suggesting that bladder transection is a suitable procedure to undertake with a high success rate in these patients.

Although a satisfactory explanation cannot at present be offered for the beneficial effects of this operation, there is no doubt that in addition to the subjective benefits obtained, there was definite objective improvement in the bladder capacity and the ability to resist urinary leakage in the majority of these patients on a regular daily basis for many months. Furthermore, it would appear from all of the published reports that relapse after a successful bladder transection is unlikely, whereas relapse after the more physiological procedure of selective sacral neurectomy has been a problem in some patients (Torrens and Hald, 1979).

It is suggested, therefore, that bladder transection has a role in the management of patients with urge incontinence associated with detrusor instability when non-operative methods of treatment have failed.

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Drug Effects on the Voiding Cystometrogram: a Comparison of Oral Bethanecol and Carbachol

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Summary—A system for objective assessment of drug activity on voiding parameters is presented. Two groups of spinal cord injured patients with reflex micturition were given bethanecol chloride 50 mg or carbachol 4 mg orally. Carbachol produced a much greater change in recorded voiding parameters.

Amongst the published data on the effect of drugs on the lower urinary tract there is remarkably little human, *in vivo*, data available. Several studies during the filling phase of the cystometrogram are reported as well as studies on the urethral pressure profile and urinary flow rates. However, studies of voiding parameters are particularly lacking due to the absence of a reproducible system to study the bladder during repeated voiding sequences. Although modern urodynamic techniques allow simultaneous measurement of detrusor pressure, flow rate and external sphincter activity, these studies cannot be repeated several times in a normal person, as would be required for drug investigation. Thus the reflex bladder of the male paraplegic patient provides a useful working model for the evaluation of drugs acting on the lower urinary tract, since the sacral reflex arcs are intact but isolated from higher centres.

We present a system to quantify several parameters of voiding function suitable for drug studies for 2 short-acting drugs. Two parasympathomimetic agents (bethanecol and carbachol) were studied and the results are presented. Both drugs are thought to have no central effect and, when administered orally, have their peak effect within one hour (Diokno and Lapides, 1977).

Patients and Methods

Twenty patients with complete supra-sacral cord lesions were studied. All patients had well established reflex micturition.

The urodynamic system (Thomas *et al.*, 1975) provides simultaneous monitoring of total bladder and rectal pressure, subtracted detrusor pressure, voided flow rate and voided volume. Two fine urethral catheters (less than 1.5 mm ED) were used, one for bladder filling and one for monitoring bladder pressure. Both catheters were left *in situ* during voiding, so allowing constant bladder filling and monitoring of repeated voiding sequences. Studies were performed with the patients in the supine oblique position.

The bladder was filled at a constant rate, the average being 20 ml/min. Each voiding cycle was recorded and the following parameters measured: voided volume, subtracted detrusor pressure, length of detrusor contractions, interval between contractions and peak flow rate. The bladder was filled constantly and repeated voiding sequences recorded until the voiding pattern became settled and reproducible. When a settled pattern of micturition had been established the patient was given either bethanecol chloride 50 mg orally or carbachol 4 mg orally on an empty stomach. One patient was given 25 mg bethanecol only as he had complained of severe sweating and palpitations following subcutaneous bethanecol. After administration of the drug the voiding parameters over repeated voiding sequences were recorded for at least a further 75 min. The patients were not moved during the procedures and were encouraged to lie still.

Results

Although measurements were made over several voiding sequences, the results are expressed as an average for each parameter both before and after drug administration. Only the voiding parameters 30 min after drug administration are reported.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

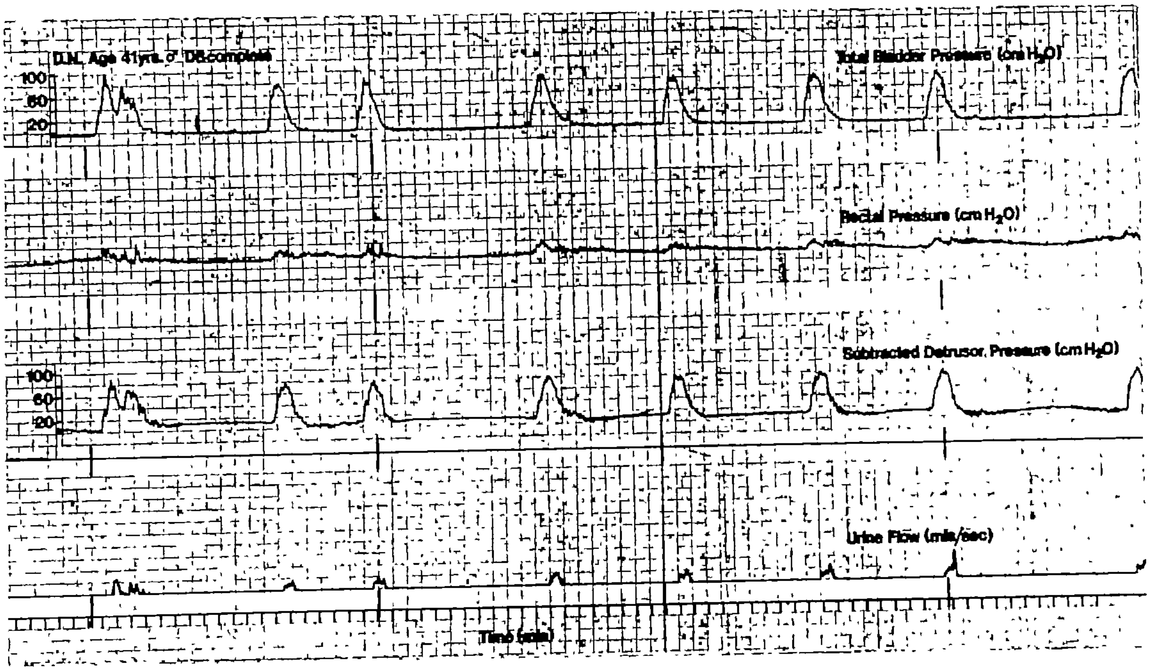

Fig. 1 Urodynamic trace in a 41-year-old paraplegic male. Constant filling at 20 ml/min.

After a period of equilibration the voiding pattern of each patient became regular and reproducible (Fig. 1). The baseline bladder pressure remained constant in all patients.

The results of the effect of bethanecol chloride have been reported to the International Continence Society in 1979 (Figs. 2 and 3). Taken as a group (10 patients), none of the measured parameters altered significantly. The greatest changes were in the voided volumes. In 2 patients the voided volumes increased by 51 and 44% respectively, but as a group the voided volume increase was only 14%. The only other parameter to alter was the frequency of detrusor contractions, which decreased by 13%.

There was a much greater change in voiding

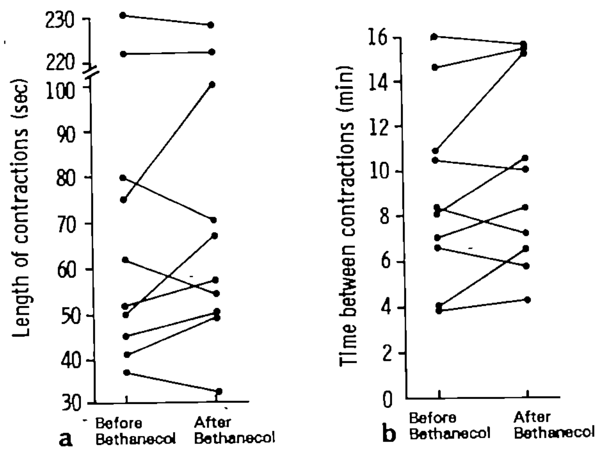

Fig. 2 The effect of oral bethanecol (50 mg) on (a) voided volumes and (b) voiding detrusor pressure. (Each point represents mean value for each patient.)

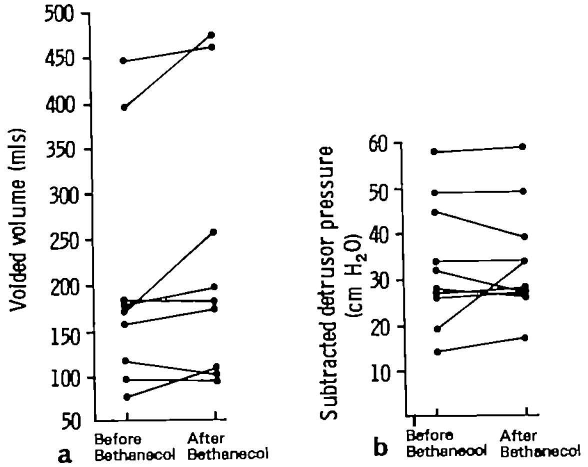

Fig. 3 The effect of oral bethanecol (50 mg) on (a) length and (b) frequency of detrusor contractions.

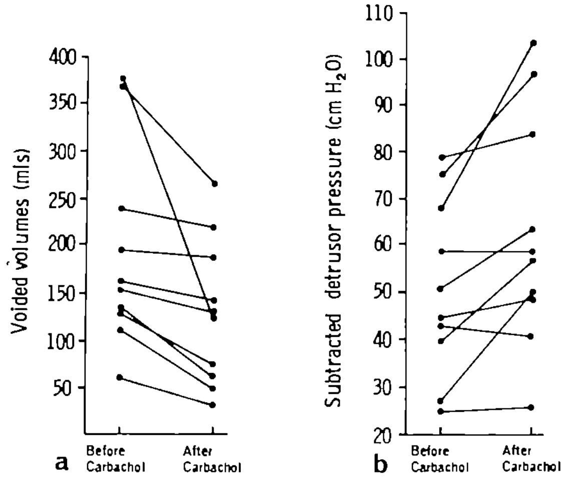

Fig. 4 The effect of oral carbachol (4 mg) on (a) voided volumes and (b) voiding detrusor pressure

parameters following carbachol administration (Figs. 4 and 5).

In all 10 patients the voided volumes decreased, the mean reduction being 34%. In 4 cases the voided volumes were reduced by 50% or more, the greatest decrease being 68%. There was not such a marked overall change in peak voiding detrusor pressure, which increased by 24%.

Detrusor contractions were considerably shortened in most patients after carbachol (average 29%), whilst the frequency of detrusor contractions was increased by 32%.

Peak voided flow rates varied very little before and after drug administration. With bethanecol the average peak flow rate was 11.5 ml/s prior to the drug and 12.3 ml/s after. Similarly, carbachol produced only a small change with an average peak flow of 11.0 ml/s before the drug and 12.0 ml/s after.

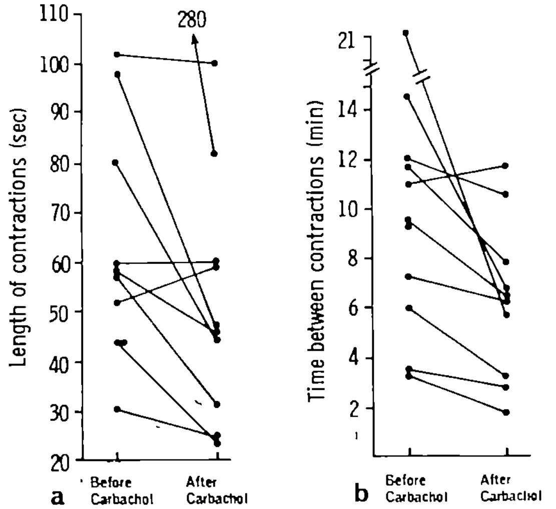

Fig. 5 The effect of oral carbachol (4 mg) on (a) length and (b) frequency of detrusor contractions

Discussion

The patients given 50 mg oral bethanecol showed little change in the various voiding parameters. This accords with previous reported work indicating very little change with an oral dose of 50 mg (Diokno and Lapides, 1977; Wein *et al.*, 1978). It has also been shown that in a denervated bladder an oral dose of 200 mg bethanecol chloride is required to produce the same effect as a subcutaneous injection of 5 mg of the drug (Lapides *et al.*, 1963). Although in the individual the response to a fixed dose will vary, it would seem that the oral dose of bethanecol chloride currently used in clinical practice is inadequate.

The group of patients given 4 mg oral carbachol showed a much greater change in voiding parameters. Overall voided volumes were reduced and the length of detrusor contractions shortened, whilst detrusor pressures and frequency of contractions were increased. It appears that detrusor contractions occurred at a smaller bladder capacity, so that the voided volumes were diminished. The bladder appears to be more sensitive to filling, initiating earlier and more powerful reflex detrusor contractions, so improving voiding efficiency in the absence of outflow obstruction.

Although the current system makes no allowance for the measurement of residual urine, we know from clinical experience that residual urines are reduced considerably by oral carbachol.

Striated muscle sphincter activity was not monitored in this series and therefore an accurate assessment of the effect of drugs on detrusor-sphincter dyssynergia was not possible.

In most cases carbachol produced low pressure rhythmical rectal contractions—one indication that the drug had been absorbed and was active.

This study demonstrated the usefulness of the male reflex bladder following spinal cord injury as a model for studying the urodynamic effects of drugs on the lower urinary tract.

Oral carbachol in a dose of 4 mg had a much greater effect on voiding efficiency than a 50 mg dose of oral bethanecol chloride.

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Urological Disability in Quadriplegia: A Study of Treatment and Follow-up in 92 patients

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Summary—The urological aspects of a series of 92 quadriplegic patients are presented. The types of operations done to relieve outlet obstruction and the long-term follow-up with particular emphasis upon the urographic findings and the incidence of pyelonephritis are described and discussed.

Vesical outlet obstruction occurs in approximately 30% of all spinal cord injury patients and occurs most frequently in thoracic lesions and with almost equal frequency in cervical and lumbar lesions (O'Flynn, 1978). The incidence is greater in complete as opposed to incomplete lesions.

Clinical studies and urodynamic investigations indicate that the sites of obstruction are located at the internal urinary orifice and at the external sphincter and that, almost invariably, dyssynergia between these 2 elements can be demonstrated. The true explanation of this functional disorder is not at present apparent.

Emmett and Dunne (1946) showed that outlet obstruction could be relieved by transurethral resection of the bladder neck and prostate (TUR) and the procedure needs to be repeated occasionally to get a satisfactory result. Transurethral resection is not always successful and it was demonstrated by Ross *et al.* (1958) that external sphincterotomy relieved the outlet obstruction when TUR failed. External sphincterotomy was later tried alone as a primary operative procedure for complete cervical lesions (O'Flynn, 1972). Lapides had demonstrated the pressures to be greatest in this area of the urethra in the normal individual (Lapides *et al.*, 1960). Later still TUR and external sphincterotomy as a combined operation was advocated (O'Flynn, 1976). All of these procedures had a failure rate which resulted in further repeat operations being done.

In cervical lesions outlet obstruction is generally more difficult to treat and multiple operations are frequently necessary. In the majority of patients satisfactory voiding and emptying are achieved. A small number of patients must be treated by continuous catheterisation (urethral or suprapubic) or possibly by diversion because of failure of outlet obstruction operations or, more usually, because of the patient's poor medical state.

Patients and Methods

This report refers to a continuous series of quadriplegics (87 males and 5 females) treated at the National Rehabilitation Centre, Dublin, during the years 1961 to 1979 inclusive. The age at time of injury ranged from 15 to 78 years, with 46 patients younger than 40 years of age, 23 patients 40 to 60 years of age, and 23 patients older than 60 years at presentation. Table 1 categorises the patients by level and degree of injury. All patients had been treated initially by intermittent or continuous urethral catheterisation and a few by suprapubic cystostomy or suprapubic catheterisation. The decision to operate after catheterisation had been stopped was based on indications previously published (O'Flynn, 1978): (1) Persisten

Table 1 Level and Extent of Spinal Lesion in 92 Patients

Level	*Extent*	*Number*
C_4	Complete	12
	Incomplete	5
C_5	Complete	19
	Incomplete	12
C_6	Complete	21
	Incomplete	10
C_7	Complete	10
	Incomplete	3

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Primary Operations for Outlet Obstruction

TUR	56 (61%)
External sphincterotomy	17 (18%)
Combined operation (external sphincterotomy and TUR)	18 (19%)
Cystostomy	1 (1%)

difficulty in micturition and in maintaining the urinary stream. (2) Inadequate bladder emptying and failure to achieve a balanced bladder. (3) Persistent urinary infection associated with a high residual urine (*i.e.* more than 120 ml). (4) Radiographic evidence of a urinary tract obstruction (*i.e.* ureterectasis and pyelectasis).

Up to 1966 most patients had a TUR, and after that external sphincterotomy was introduced and became more common. The primary operations performed are shown in Table 2. The one patient who had a suprapubic tube was a 74-year-old man whose medical condition precluded any further treatment.

If, after the initial operation, voiding was not satisfactory, a second operation was done, either repeating the original procedure or changing the site of operation to the external sphincter.

Thus the series includes a number of patients in whom TUR was performed first, followed by external sphincterotomy or *vice versa*. In the later part of the series TUR and external sphincterotomy were done as a combined operation. As previously noted, a second operation was frequently necessary to achieve a balanced bladder which emptied satisfactorily. All of the operations were done by the same surgeon (D.O'F.).

While in the hospital each patient was followed with weekly urine cultures and routine intravenous urograms—the number of which was determined by their genitourinary status.

In this series all of the patients were discharged voiding satisfactorily and were followed up by routine urological review at the Centre. The initial review was usually done at 3 months and then on a 6- to 12-monthly basis after that. Any patient seen in follow-up who had pyeloureterectasis or poor emptying on the cystogram phase of his IVU was re-evaluated endoscopically.

Table 3 Outlet Obstruction in Quadriplegia: Repeat Operations after TUR in 56 Patients

Secondary operations	34 (61%)
TUR prostate	16 (29%)
External sphincterotomy	15 (27%)
Combined	3 (5%)
Tertiary operations	14 (41%)

Table 4 Outlet Obstruction in Quadriplegia: Repeat Operations after External Sphincterotomies in 17 Patients

Secondary operations	9 (53%)
Transurethral prostatectomy	5 (29%)
External sphincterotomy	4 (24%)
Combined	0
Tertiary Operations	5 (29%)

Results

Complete follow-up was available on all 92 patients. Thirty-eight patients were followed for less than 5 years, 38 for 5 to 10 years and 16 for more than 10 years. Table 3 shows the repeat operative intervention necessary in the 56 patients who initially underwent TUR. Tables 4 and 5 show repeat operative intervention in the patients who underwent external sphincterotomy and external sphincterotomy along with transurethral prostatectomy respectively.

Thirty-three (87%) of the patients who were followed for less than 5 years had normal intravenous urograms. For those followed from 5 to 10 years there were 30 (79%) normal pyelograms while 9 of the patients followed for more than 10 years (56%) had normal intravenous urograms (Table 6). Two of the patients who developed pyelonephritis after 10 years had indwelling urethral catheters for a long period of time; one for recurrent urethral strictures had a suprapubic cystostomy for 2 years and the other had an indwelling urethral catheter for over a year for a urethrocutaneous fistula. It was only after this period of long-term indwelling catheter that they developed pyelonephritis. One of the patients who developed pyelonephritis in the 5- to 10-year follow-up also had a long-term indwelling urethral catheter which was followed by chronic pyelonephritis. He also had a urethrocutaneous fistula.

Information with respect to sterility of urine was available on all patients. The result of the

Table 5 Outlet Obstruction in Quadriplegia: Repeat Operations after Combined Procedures in 18 Patients

Secondary operations	9 (50%)
TUR	3 (17%)
External sphincterotomy	2 (11%)
Combined	4 (22%)
Tertiary operations	4 (22%)

Table 6 Intravenous Urogram Findings on Follow-up in 92 Patients

Length of follow-up	*Normal (%)*	*Abnormal*	
Less than 5 years (38 patients)	33 (87%)	Pyeloureterectasis	2
		Upper tract stone	1
		Pyelonephritis	2
5-10 years (38 patients)	30 (79%)	Pyeloureterectasis	2
		Upper tract stone	3
		Pyelonephritis	3
Over 10 years (16 patients)	9 (56%)	Pyeloureterectasis	0
		Upper tract stone	0
		Pyelonephritis	7

most recent urine culture was used. If the patient had had a recent urinary tract infection but was now sterile on treatment this was classified as sterile. Urine was sterile if no growth was obtained either on a mid-stream specimen of urine or a catheterised specimen. Using these criteria, 40 patients (44%) had infected urine, 44 (47%) had sterile urine and 8 (9%) had sterile urine while on treatment. The most common organisms cultured were *Esch. coli* and *Proteus* species, both indole positive and negative.

Nineteen patients had urological complications (Table 7). Only 8 patients ultimately required permanent indwelling catheters. Three of these were elderly men who underwent suprapubic cystostomy, 1 for stricture disease, 1 for inability to maintain a condom catheter, and 1 for persistently raised post-micturitional residual urine. Five patients had indwelling urethral catheters—2 for autonomic dysreflexia, 2 for chronic urinary retention, and 1 to allow a pressure sore to heal.

There were 22 deaths in the series (24%). The average age at presentation of those patients who died was 58 years. Of the 22 deaths, 19 were in patients who were over 50 years old when injured, and 11 of these patients were actually older than 60 when they first presented. A definite cause for the death of these patients was available in only 12 cases. This may be due in part to the fact that many of these patients were from rural areas where exact documentation of cause of death was not available. Pneumonia was the leading known cause of death (6 patients), with 4 dying of gastro-intestinal disease, 1 of uraemia after transurethral prostatectomy, and 1 secondary to sepsis from a pressure sore.

Table 7 Urological Complications

Upper tract calculi (2 ureterolithotomies, 2 pyelolithotomies, 1 nephrectomy)	5
Urethrocutaneous fistula	6
Urethral diverticula	2
Urethral strictures (1 suprapubic cystostomy, 1 vesicostomy, 2 dilatation only)	4

Table 8 Outlet Obstruction in Quadriplegia Intravenous Urogram at Time of Death in 22 Patients

Follow-up	*Number of patients*	*Normal IVUs*
<5 years	15	12
5-10 years	6	4
>10 years	1	1

Table 8 shows the status of the IVU at the time of death in these patients. It can be seen that 17 of the 22 patients (77%) had normal IVUs at the time of death.

Discussion

Over the past 3 decades the urological management of the traumatically paralysed patient has been a subject of much discussion in many publications. Many authors have implicated renal failure as the most common cause of death, in the long term, in this unfortunate group of patients (Tribe, 1963; Nyquist and Bors, 1967).

The upper tract changes, which lead to renal failure, result from an imbalance between the expulsive forces of the detrusor muscle and the forces maintaining urinary continence. The goal of urological rehabilitation is to create a situation in which the detrusor empties at low pressure and without impedance from these forces. Recent knowledge has emphasised the high incidence of dyssynergia between the detrusor and the external sphincter as a cause of obstruction in the paralysed patient. This may explain the fact that 61% of the patients in this series originally treated with transurethral prostatectomy had to have repeat operations. Similar figures were obtained by Schellhammer *et al.* (1974) who found that of 30 patients who had undergone unsuccessful procedures for the lowering of urethral resistance, 28 had had a transurethral prostatectomy. All of these patients later underwent sphincterotomy with success. It should be noted that 53% of the patients with external sphincterotomies and 50% of those with combined procedures had to have further operations. This could be due to residual prostatic tissue, stricture formation, inadequate resection of the sphincter, possible re-growth of the sphincter, or other factors, not completely understood, which are important in urethral resistance. The important point to appreciate is the possible need for repeat operations when following these patients (O'Flynn, 1974).

The main criterion used to determine the efficacy of treatment at the National Medical Rehabilitation Centre is the intravenous urogram. The number of patients with pyeloureterectasis (4.3%) compares favourably with Scher's figure of 17.5% for quadriplegics, although no definite follow-up was given in his series (Scher, 1975). Scher did have a 6% incidence of chronic pyelonephritis in quadriplegics as opposed to the current series overall rate of 11%. When comparing Scher's 13% incidence of chronic pyelonephritis in all patients followed for less than 4 years (quadriplegics and paraplegics), the present series compares favourably with an incidence of 5.3%. One of the disturbing factors was the decrease in normal urograms as length of follow-up increased. Concomitantly with this, the rate of pyelonephritis rose from 5% at less than 5 years to 7% at 5 to 10 years, and to 44% at more than 10 years. This may be due in part to the fact that patients cannot, because of practical considerations, be evaluated at the National Medical Rehabilitation Centre each time they have a bout of acute pyelonephritis. Such events may establish a focus of infection leading to areas of chronic pyelonephritis. As noted, 3 of the patients who developed pyelonephritis did have long-term indwelling urethral catheters prior to developing this problem.

The low incidence of upper tract stones (4% overall) and the fact that only 5 operations for such had to be performed is encouraging.

The current series has not dealt with reflux specifically and these patients were not routinely evaluated for this. If reflux results from chronic infection and micturition at high intravesical pressure, then it is a sequel of outlet obstruction and not an entity in itself. Thus, dealing with the outlet obstruction should alleviate both infection and reflux. The increasing incidence of chronic pyelonephritis and the infection rate of 44% are again reminders of the need for constant vigilance in these patients.

In another series of long-term follow-up it has been shown there is an increase in percentage survival concurrent with descent of the level of injury and, in addition to this, as one would expect, the majority of the patients who survived long term were relatively young when injured (Nyquist and Bors, 1967). The average age, at the time of injury, of the patients who died in this series was 58 years. The overall death rate of 24%, if viewed in terms of this advanced age when injured, compares favourably with other series.

If the mortality and morbidity figures from 20 to 30 years ago (Donnelly *et al.*, 1972) are compared with those of the present day, it is evident that the improved management of the lower tract obstruction has resulted in great advances in upper tract preservation.

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The Effect of Distigmine Bromide on Voiding in Male Paraplegic Patients with Reflex Micturition

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Summary—The effect of parenteral and oral distigmine bromide on voiding efficiency in 23 male spinal cord injured patients is described. The parenteral preparation of the drug improved voiding efficiency.

Objective evidence of improved voiding efficiency with pharmacological agents is difficult to obtain. Up to now, choline esters such as bethanechol chloride and carbachol have been the main agents used to improve detrusor activity. The alpha adrenergic blocking agent, phenoxybenzamine, has also been used for its action in reducing bladder outlet resistance.

In this series we have studied the effects of the long acting anticholinesterase, distigmine bromide, on voiding efficiency in male paraplegic patients.

Patients and Methods

Twenty-three male patients with suprasacral spinal cord injury were included in this trial. They all had reflex detrusor activity producing involuntary voiding. The majority had complete neurological lesions. Two of the patients were tetraplegic. Their ages ranged from 15 to 61 years with an average age of 33 years.

The majority of the patients (14) were managed initially with an indwelling catheter which was usually removed at approximately 12 weeks post-injury to try to establish reflex voiding. If this failed, further attempts to remove the catheter were carried out at regular intervals. A further 8 patients were managed by intermittent catheterisation until voiding was established. One patient had a suprapubic catheter inserted which was clipped and released until voiding took place, so allowing the additional advantage that residual urines could be measured without passing a urethral catheter.

Once voiding had been established, patients with persistently high residual urines were selected for this trial. Included also was a small group of 5 patients who, despite repeated attempts to remove their catheter, failed to void. They had, however, been shown to have some reflex detrusor activity on a filling cystometrogram.

The parameters measured were volume voided and residual urine which, added together, gave bladder capacity. A single measurement of voided volume and residual urine is of little significance in cord injured patients since these can alter considerably because of a variety of factors—for example, time of the day, position and activity of the patient and in relation to a bowel action. Therefore, multiple voided volume and residual urine measurements were made at varying times during the day for at least a week.

Spontaneous voided volume was first measured, followed by triggered voided volume usually initiated by suprapubic tapping which may stimulate a reflex detrusor contraction. The residual urine was then measured. This was done by experienced nursing staff on the spinal injury unit using a strict aseptic technique.

Voided volumes and residual urines were measured for at least a week before any drug was given. Once satisfied that the residual urines were consistently high, distigmine bromide was given intramuscularly at the recommended dose of 0.5 mg daily for one week. The estimations of voided volume and residual urine were continued whilst the patient was on the drug and for at least one week after it had been stopped. The mean for each parameter was determined before, during and after drug administration.

The 23 patients used in this trial were divided into 3 groups; the first 2 groups consisted of 18 patients who were all voiding but had persistently high residual urines. The first group was given parenteral distigmine only and the second group

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

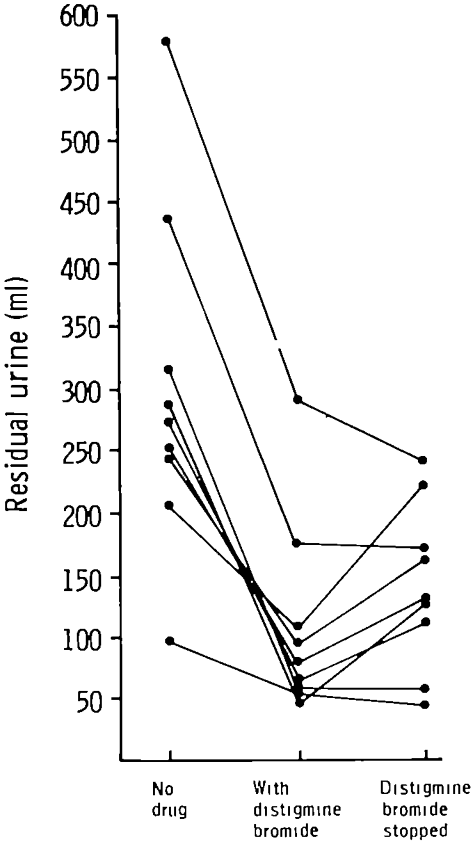

Fig. 1 Group 1. Effect of parenteral distigmine bromide on residual urine. (Each point represents the mean value for each patient.) Mean percentage reduction in residual urine 63%.

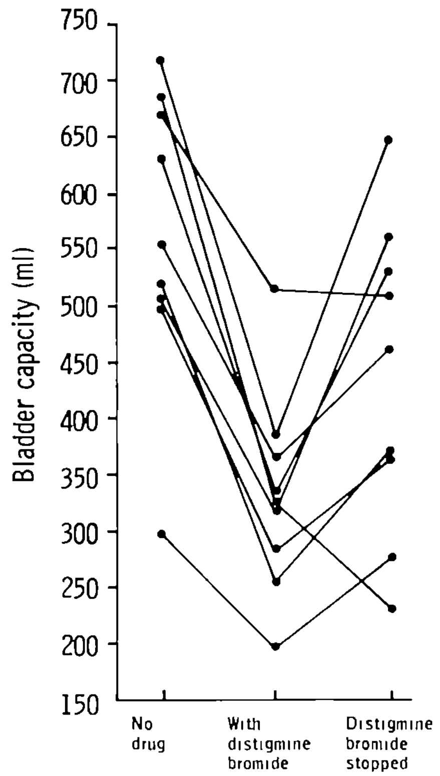

Fig. 2 Group 1. Effect of parenteral distigmine bromide on bladder capacity. Mean percentage reduction in bladder capacity 41%.

parenteral distigmine followed by the oral preparation (5 mg on an empty stomach). The third group consisted of 5 patients who had failed to void despite several attempts to remove the catheter, despite the presence of weak reflex detrusor activity on the cystometrogram.

Results

Group 1. Patients Given Parenteral Distigmine Bromide Only (9 cases) (Figs. 1 and 2)

In all 9 cases the residual urine was markedly reduced by the parenteral administration of distigmine—in 7 cases it was reduced by 50% or more. In some cases there was a remarkable reduction, *e.g.* one patient's average residual urine fell from almost 300 ml to less than 50 ml. Surprisingly, when the distigmine was stopped, in 4 cases the residual urine remained at roughly the same level as during drug administration. In only one case did the residual urine return to the level noted before administration of the drug.

Voided volumes did not necessarily increase during administration of distigmine. More significantly, in every case the bladder capacity was markedly reduced, average reduction being 41%. This lack of change of voided volumes was related to the reduction in bladder capacity and reduction in residual urines. After stopping distigmine the bladder capacity tended to increase again, but in only 2 cases did it return to the volume found prior to drug administration. Figure 3 shows one patient who was typical of the group.

Group 2. Patients Given Parenteral Followed by Oral Distigmine Bromide (9 cases) (Figs. 4 and 5)

As in Group 1, there was again a marked reduction in residual urine following intramuscular administration of distigmine. In all except 2 cases there was a reduction in residual urine of 40% or more (average 56%).

After one week of parenteral distigmine the drug was then changed to the oral preparation.

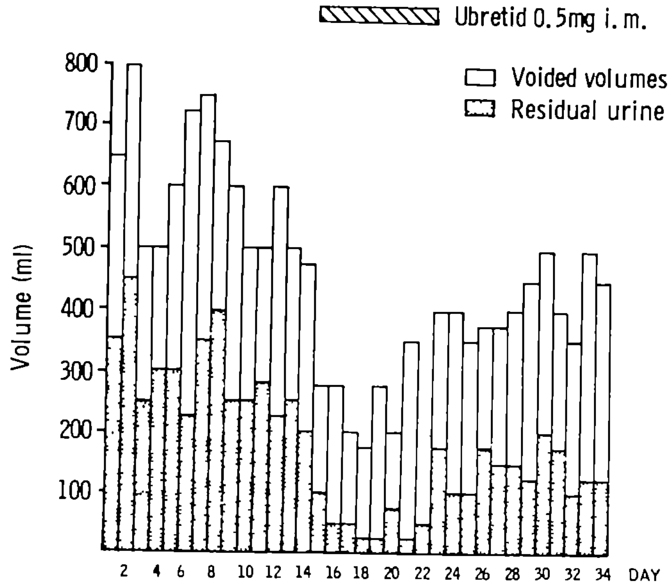

Fig. 3 The effect of parenteral distigmine bromide on residual urine and bladder capacity. Patient P.W., male aged 22 years. Complete D8 lesion.

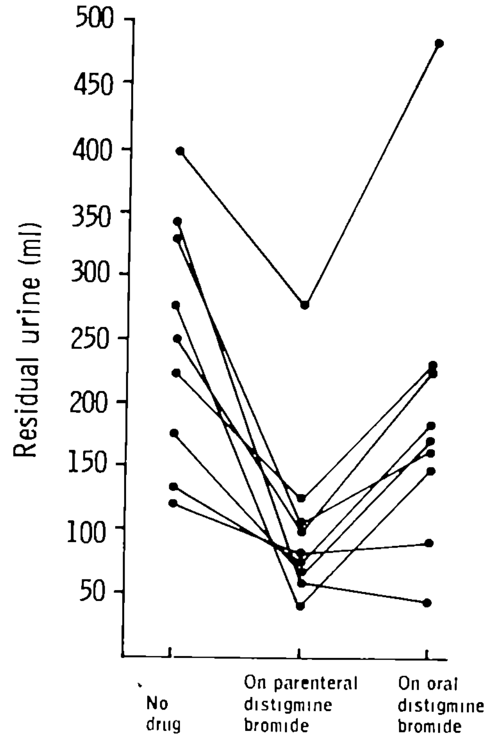

Fig. 4 Group 2. Effect of parenteral followed by oral distigmine bromide on residual urine. Mean percentage reduction in residual urine 56%.

Despite being on the oral preparation 7 of the patients' residual urines increased significantly and in only 2 cases did they remain low. Of particular interest was N.A. (Fig. 6) whose residual urine was markedly reduced on parenteral distigmine but then increased to its previous level when changed to the oral preparation. However, once intramuscular distigmine was restarted the residual urine again fell.

As in Group 1, the bladder capacity was decreased with parenteral distigmine—the average reduction being 34%. Once again voided volume was very variable. When oral distigmine was started bladder capacity tended to rise, although in 2 cases it actually decreased. Statistically the results in Groups 1 and 2 are highly significant.

Group 3. Patients Not Voiding and Given Intramuscular Distigmine Bromide (5 cases)

Each patient was started on distigmine 0.5 mg daily intramuscularly and then 2 days later the catheter was removed. Distigmine was continued for a further week before being stopped. In each case there was reflex voiding on catheter removal. Initially the residual urine volumes were high but they rapidly decreased to levels of about 50 to 100 ml. When distigmine was stopped all of the patients continued to void significant quantities; their residual urine volumes did tend to rise but not to unacceptably high levels except for one case. In this case, the videocystometrogram showed

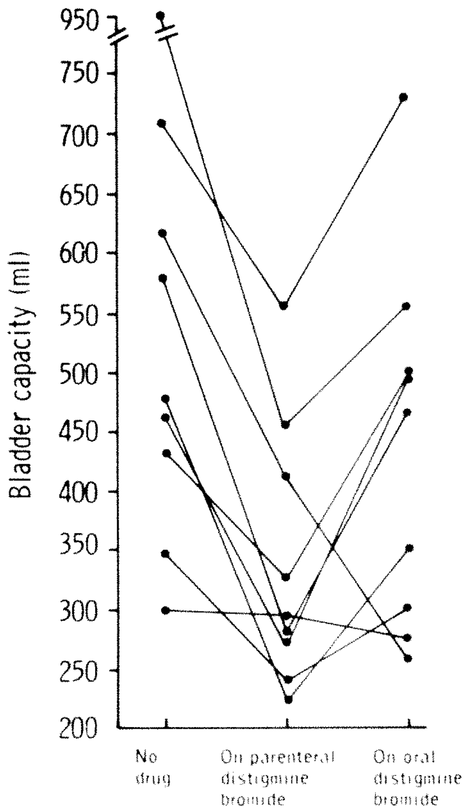

Fig. 5 Group 2. Effect of parenteral followed by oral distigmine bromide on bladder capacity. Mean percentage reduction in bladder capacity 34%.

very marked detrusor-sphincter dyssynergia subsequently requiring transurethral sphincterotomy. All 5 patients have continued to void satisfactorily. We have not yet encountered a patient who has failed to void after being given a trial of voiding with distigmine.

Side effects

Nine of the 23 patients developed side effects on parenteral distigmine. Eight patients complained of sweating; in some this was profuse and uncomfortable, but in most cases it was tolerated until the course was completed. Four patients had vomiting, diarrhoea and felt ill. Distigmine was stopped in these cases before the planned course had been completed. These patients remained in the trial as their voiding pattern had altered significantly despite their being on the drug for a shorter period of time.

Discussion

In Groups 1 (parenteral only) and 2 (parenteral followed by oral) there was a marked reduction in the residual urine volume in all cases when parenteral distigmine was given. In nearly every case this residual volume fell to acceptable levels. It is interesting to note that when distigmine was stopped the residual volumes tended to increase

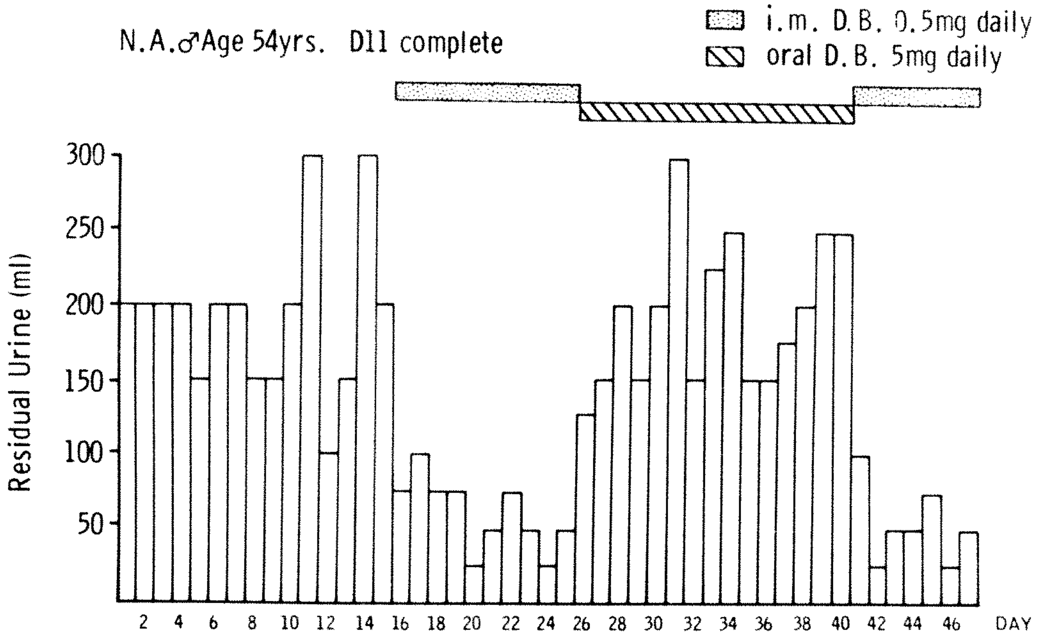

Fig. 6 The effect of parenteral and oral distigmine bromide. Histogram of daily residual urine.

but, in nearly all cases, not to the levels prior to drug administration. In fact most remained at an acceptable level of approximately 100 ml.

In Group 2 (parenteral followed by oral), when distigmine was changed from the parenteral to the oral preparation the residual volumes tended to increase but in general not to the levels found prior to parenteral administration of the drug. These results are very similar to those in Group 1 (parenteral only) when distigmine was stopped. It would therefore seem that oral distigmine at the recommended dosage of 5 mg is not as effective as the parenteral preparation, the most likely reason being that it is poorly absorbed in its active form from the gut.

Bladder capacity, like residual urine volumes, was markedly decreased when parenteral distigmine was given and then increased when the drug was stopped or changed to the oral preparation.

Parenteral distigmine, therefore, improves voiding efficiency but the mechanism of this improvement is unknown. Current urodynamic studies may help to reveal the nature of its action.

Further evidence of the action of distigmine is seen in Group 3, where patients had reflex detrusor activity but no spontaneous voiding. Distigmine improved detrusor function and so promoted voiding. Our preliminary urodynamic studies indicate that it acts by increasing the reflex voiding detrusor pressure. These results differ from the findings of Smith *et al.* (1974), whose patients were given a single dose of parenteral distigmine within 3 months following cord injury—they all failed to void.

It is concluded that parenteral distigmine bromide is a useful drug for enhancing detrusor activity, so improving voiding efficiency. It is not without side effects. Oral distigmine in the recommended dosage was of little value in improving detrusor function in the patients studied in this series.

Acknowledgements

We wish to thank Mrs K. Jones for secretarial work and the Department of Medical Illustration for preparation of the tables.

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Survival of Transitional Cell Carcinoma Cases in 2 Yorkshire Centres

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Summary—The survival of all cases of bladder cancer presenting in residents of the Huddersfield and Bradford Health Districts has been computed. Cases arising in the 2 districts have been contrasted using a sequential log rank survival method and an excess of deaths in early stage tumours is noted to have occurred in Huddersfield. The reasons for this are discussed.

Attention has been drawn to bladder cancer in West Yorkshire by the high mortality figures published in 1978 by the Office of Population Censuses and Surveys. These indicated that the bladder cancer mortality for males and females in Huddersfield was extremely high for people of working age for the period 1969 to 1973, whilst the corresponding figures for Bradford were much less (Standardised Mortality Ratios in males: Bradford 80 and Huddersfield 244).

As part of a programme of epidemiological research designed to investigate this, we have examined more recent data and have found that the crude incidence figures for Huddersfield are high for males and females but the results for Bradford are also unexpectedly high, though not quite as high as those from Huddersfield (27/100,000/yr males for Bradford and 31/100,000/yr males for Huddersfield, and 11/100,000/yr females for Bradford and 13/100,000/yr females for Huddersfield). It seemed possible, therefore, that the disproportionately increased mortality seen in Huddersfield might have been due to differences in survival and this has been investigated further in this paper.

Methods

All known cases of transitional cell carcinoma of the urothelium (ICD8:188 and 223) were collected for the 3 years 1975 to 1977 using a variety of overlapping sources which included the cancer registry records, histopathology reports, personal patient lists, Coroner's notifications and death certification. All of the hospital case notes were carefully perused and only histologically proven cases included. The following information was collected: name, address, sex, date of birth, age at onset, site of tumour, clinical state (UICC, 1978) and outcome on 1 April 1980. The date and cause of death were recorded or their present clinical status was noted.

These data were carefully coded and analysed using the log rank method of Peto *et al.* (1976, 1977). The data were analysed for total survival and not censored according to the death certificate information.

Results

In the series there were 374 cases: 231 from Bradford (175 males and 56 females) and 143 from Huddersfield (96 males and 46 females); 367 cases had tumours arising in the bladder epithelium but 2 from Bradford and 4 from Huddersfield had renal pelvic tumours and one case from Huddersfield had a primary ureteric tumour. Note the relatively high incidence of female patients in the Huddersfield series.

This study was aimed at examining the totality of disease experienced within 2 defined areas and

Table 1 Survival of Bladder Cancer Cases Taking Particular Variables Into Account

Variable	χ^2 *value*	*Probability*	*Significance*
Sex	1.74	0.1873	NS
Age at diagnosis	27.34	0.0001	Significant
Stage at diagnosis	171.68	0.0001	Significant
Place	7.13	0.0076	Significant

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includes several patients not fit to be treated, so that the survival statistics include all patients with the disease in the 2 areas.

The overall survival rate, irrespective of centre, shows that at 1 year 72% survive, at 2 years 63% survive, and at 5 years 57% survive. The survival of the entire series by sex, age and stage at diagnosis is shown statistically in Table 1. In general terms sex differences do not influence the overall outcome of the disease, although males tend to survive slightly longer than females. Age and stage, however, appear differentially to alter survival in a statistically significant fashion. The younger survive longer than the older age groups and, as expected, those with early stage disease have a longer survival than those with the later stages. The differences between survival for Huddersfield and Bradford are also statistically significant, with overall the Huddersfield cases having a 12%, 11% and 15% worse survival at 1, 2 and 5 years.

Could this be due to differences in stage or age at presentation with an excess of the poorer prognosis cases occurring in Huddersfield? Tables 2 and 3 show the proportion of cases from the 2 centres subdivided by stage and age at presentation. There is little difference between age distribution, with slightly more younger cases occurring in Huddersfield. The stages tend to be less favourable overall for the Huddersfield cases, however, with a greater proportion of stage 2, 3 and 4 cases. Studies on delay times to diagnosis indicated that cases presented an average of 2 months earlier in Huddersfield compared with Bradford. This should mean one might expect fewer, not more, late stage cases in Huddersfield.

The differential survival is examined statistically between the 2 centres in Table 4, taking age and stage into account. The summary statistics given in this table show a series of χ^2 values together with their levels of significance. Unlike some other statistical tests, these results are best interpreted by examining the actual χ^2 value. The summary survival differences between Huddersfield and Bradford result in a χ^2 value of 7.13 (Table 1); when account is taken of age this is slightly reduced to 4.85, but there is still a significant difference between the 2 centres. This difference disappears when stage is taken into account, but the χ^2 value does not become nearly zero, which suggests that although stage is the major factor, other factors such as age differences might contribute. In summary, therefore, these results indicate that the differences in age distribution are not sufficient to explain away the poorer survival of the Huddersfield cases. The differential survival by different stages, however, accounts for much of the disparity. A close examination of the comparative survival of cases from Huddersfield and Bradford, stage by stage, shows that the survival of stages 2, 3 and 4 are similar between the 2 centres and the majority of the differences between the 2 series are due to the poorer survival of stage 1 cases. This would seem to indicate that any difference between the 2 urology departments are real and not due to individual variation in staging.

Table 2 Stage At Presentation

	Huddersfield		*Bradford*	
	N	*%*	*N*	*%*
1	46	37	107	51
2	26	21	31	15
3	34	27	47	22
4	20	16	25	12

Table 3 Age At Presentation

	Huddersfield		*Bradford*	
	N	*%*	*N*	*%*
<40	2	1	3	1
40-49	3	2	8	4
50-59	35	26	42	19
60-69	41	30	79	35
70-79	43	32	78	34
>79	12	9	17	7

In the Bradford series there were 4 stage 1 deaths (4%) and in Huddersfield there were 9 (20%), a remarkable differential resulting in a 20% difference in survival at 5 years. All of the Bradford deaths were due to diseases other than cancer, whilst in Huddersfield there were 4 deaths from non-malignant disease, 3 deaths from other malignancies and 2 due to bladder cancer.

Table 4 Survival of Bladder Cancer Cases Between the 2 Centres Taking Account of Age and Stage

Variables	*χ^2 value*	*Probability*	*Significance*
Place by age	4.85	0.0276	Significant
Place by stage	1.88	0.1703	NS
Place by age and stage	0.89	0.3444	NS

Discussion

Huddersfield has more patients who present in the worse prognosis groups despite the fact that the Huddersfield cases are diagnosed slightly earlier after the onset of the symptoms than Bradford cases by an average of 2 months. Despite this, the overall survival rates exceed those quoted by Waterhouse (1974) from Birmingham.

Even when all of the differences that might alter survival in the 2 series are accounted for, there is still a marked difference, in particular in early stage disease where there appears to have been about 7 to 8 more deaths than expected.

The slightly younger age range, the later stages despite early presentation and the poorer prognosis of apparently milder cases suggest that bladder cancer in Huddersfield may have unknown biological differences when contrasted with bladder cancer in Bradford.

Thirteen patients with stage 1 disease died: 4 from Bradford and 4 from Huddersfield died from other causes but the remaining 5 from Huddersfield died from malignant disease. Two of the 5 died as a direct result of bladder cancer, both having had carcinoma *in situ* changes in addition to well differentiated papillomata of the bladder. The other 3 deaths were as a result of lung cancer, stomach cancer and a clear cell carcinoma of the kidney.

Huddersfield stage 1 cases are quite different from Bradford, possibly due to the different aetiological possibilities available in Huddersfield, and this is the subject of a separate investigation. The other consideration is that there are more carcinoma *in situ* cases in Huddersfield and these, by convention, have been classed along with the stage 1 cases. The dual malignancies could all be related to occupational exposure to carcinogens and the 2 carcinoma *in situ* cases both have a background which would have exposed them to Benzidene or 2-Naphthylamine. These unusual cases account for the survival differences between the 2 centres.

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TNM (1978) in Bladder Cancer: Use and Abuse

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Summary—Modifications to the TNM classification for bladder cancer, introduced in 1979, are described.

The use of this classification was evaluated in 106 new patients. It proved to be satisfactory for *in situ* and papillary tumours but major problems occurred in attempting to separate superficially invasive from deeply invasive tumours.

Several aspects of this classification require further consideration and modifications are proposed.

The TNM system for the classification of malignant tumours has continued to evolve since its original description by Denoix (1944). As a result of the deliberations of various committees and persons interested in the subject, the first UICC booklet on the TNM system was published in 1968. This booklet classified 23 tumours and it was recommended that the classification proposals should be subjected to a 5-year trial period and that they should then be reviewed. The second edition of the booklet was produced in 1974 and contained some new tumours as well as amendments to the previously published classifications. An appraisal of the 1974 classification for urological tumours was made by Wallace *et al.* (1975) (Fig. 1) who emphasised that this was not the definitive classification for these tumours and that the TNM system was one which depended upon the co-operation, guidance and advice by those clinicians who were intimately involved in the application of the system to a particular site.

A third edition of the UICC booklet appeared in the autumn of 1978, to be effective from 1 January 1979. In recognition of the opinion expressed by clinicians not to introduce changes too often, it is intended that the 1978 classification should remain unchanged for at least 10 years, unless good reasons to make a change are evident.

The changes that were introduced in the third edition of the UICC (1978) booklet and our experience with this classification for bladder cancer since January 1979 form the basis of this report.

TNM (1978) Bladder

A full description of the tumour classification is given in the Appendix. The following changes were introduced into the 1978 classification:

(1) T1 tumours are separated into Ta and T1 tumours (Fig. 2). Thus, a Ta tumour is the papil-

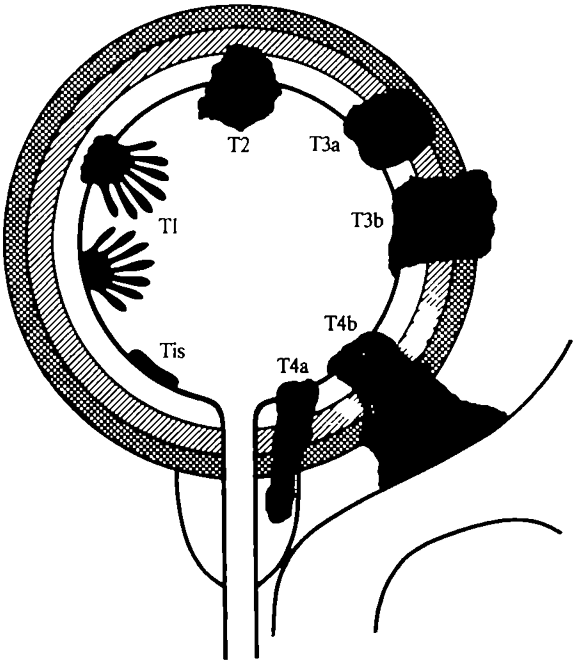

Fig. 1 T category for bladder cancer: 1974 classification.

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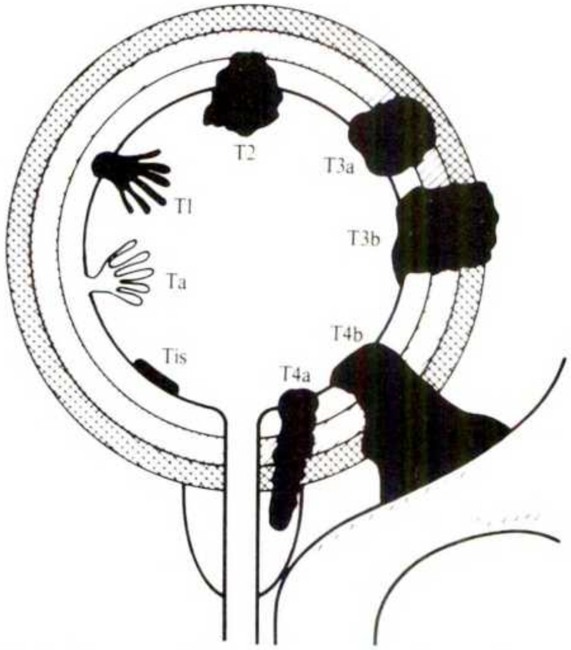

Fig. 2 T category for bladder cancer: 1978 classification.

lary non-invasive carcinoma whose previous designation was T1 Pis. The Ta tumour now corresponds to the Stage 0 tumour of the Marshall modification of the Jewett bladder tumour classification (Marshall, 1952) (Fig. 3). A T1 tumour is a superficial tumour with invasion of the lamina propria only and was previously designated T1 P1. This T1 tumour now corresponds to the Stage A tumour of the Marshall modification of the Jewett classification (Fig. 3).

(2) Two classifications are described for each site, namely:

(i) Pre-Treatment Clinical classification, designated TNM. This is based on evidence acquired prior to the decision as to definitive treatment. Such evidence arises from clinical, radiological, endoscopic and other relevant findings. In some instances it may be based additionally on the evidence derived from *surgical exploration prior to the decision as to definitive treatment.*

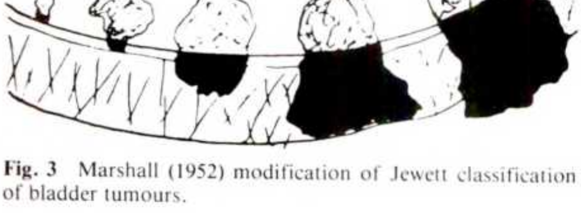

Fig. 3 Marshall (1952) modification of Jewett classification of bladder tumours.

(ii) Post-Surgical Histopathological classification, designated p.TNM. This is based on the evidence acquired prior to the decision as to definitive treatment, supplemented or modified by the additional evidence acquired from *definitive surgery and from the examination of the therapeutically resected specimen.*

Patients and Methods

One hundred and six sequential new cases of bladder cancer were studied and classified according to the TNM (1978) recommendations. All cases had multiple mucosal biopsies according to the recommendation of Wallace *et al.* (1979). Thus biopsies were taken from the right and left walls, the dome and base of the bladder using the Storz cup biopsy forceps. The tumour was biopsied either by the cup forceps or by the resectoscope. Usually small papillary lesions were removed with biopsy forceps and the base of the tumour diathermised. Larger tumours were usually resected either completely if the operator considered this to be the definitive treatment or, if the tumour was thought to be too large for complete removal, partially, in order to obtain adequate tissue for histopathology.

Bimanual examination under general anaesthesia following endoscopy was always made by at least one member of the senior staff.

The histopathology and clinical details of all patients were reviewed at a weekly combined pathological-urological-radiotherapy meeting.

Results

The *clinical* assessment of the tumour was made according to the endoscopic and bimanual findings and 5 groups were recognised: flat, papillary, invasive i (?superficial muscle), invasive ii (?deep muscle) and fixed. These findings were then correlated with the pathological pT category (Table 1).

The results showed:

(1) Although most of the flat lesions proved to be *in situ* tumours, 2 were more advanced.

(2) Of 68 papillary tumours 49 were correctly assessed, though the distinction between Ta and T1 was made only from the histopathology; 4/68 were pT2 and of these 2 were probably pT3; 15/68 were labelled pTX, usually because of inadequate tissue for the histopathological assessment, *i.e.* the biopsies being too superficial or too traumatised by diathermy.

Table 1 Correlation Between Clinical Assessment of Tumour and pT Category in 106 Cases of Bladder Cancer

	pTis	*pTa*	*pT1*	*pT2(+)*	*pT3*	*pTX*
Flat (7)	5	0	1	0 (1)	0	1
Papillary (68)	0	26	23	4 (2)	0	15
Invasive i (13)	0	2	4	3 (2)	0	4
Invasive ii (16)	0	1	6	0 (3)	0	9
Fixed (2)	0	0	0	0 (2)	0	2

(3) No patient was judged pT3 because none of the specimens comprised the full thickness of the bladder wall. However, there were 10 patients where the pathological report was "at least pT2"—designated pT2 (+) in Table 1; these patients are also included in pTX category since, by definition, "the extent of invasion cannot be assessed". (4) Thirteen patients thought to have a tumour invading the muscle were either pTa or pT1.

The correlation between the clinical assessment and pathological category showed a 70% agreement for *in situ* and papillary lesions but a very poor agreement for the other clinical groups (Table 2). These results also show that pTX is an unsatisfactory category because the pathologist can often give a helpful guide to the extent of invasion, even though he cannot determine the full extent; thus in 11 patients the tumour invaded superficial muscle and might have extended into deeper muscle but it was not possible to be sure from the biopsy provided.

The correlation between the clinical assessment and the G category (Table 3) shows that all but 3 in the invasive groups had either G2 or G3 cell grades.

Discussion

This study attempted to evaluate the revised TNM (1978) classification for bladder cancer when applied to a general urological department which has a close liaison with a regional radiotherapy department. We were very aware within our own unit and among other departments of the hospital that the TNM classification could be unwittingly misused. The ready availability of the booklet has been necessary to check regularly the variation in interpretation of the classification. Joint meetings for reviewing histology and assessing the patients at endoscopy sessions have proved of great value to both junior and senior staff.

It must be admitted that both the terminology and the concept of pT is unsatisfactory in its use with bladder cancer. A specimen of the whole tumour with the full thickness of bladder wall would certainly allow for precise histopathological classification, but it is now exceptional to carry out a partial cystectomy and uncommon to carry out a total cystectomy without adjunctive radiotherapy. Thus this ideal requirement can rarely be met. The definitive surgery of bladder tumours usually means a transurethral resection, so that material from this procedure must continue to be the main source for pathological assessment.

In practice it is confusing to have a pathological component in the T classification as well as in the pT classification. It is impossible to distinguish, clinically, a Ta from a T1 tumour and since this separation under the pre-treatment heading is misleading, a single category Ta/T1 is recommended. Likewise, it was found that attempts to distinguish T2 from T3 (especially T3a) tumours were usually frustrated. A complete resection of smaller tumours is entirely possible and provides both definitive treatment and good histological

Table 2 Correlation Between Clinical Assessment and pT Category

Clinical assessment	*Clinical/pathology agreement*	*pTX*	*pT2(+)*	*Other pT*
Flat (7)	5 (71%)	1	1	1
Papillary (68)	49 (72%)	15	2	4
Invasive i (13)	3 (23%)	4	2	6
Invasive ii (16)	0 (0)	9	3	7
Fixed (2)	0 (0)	2	2	0

Table 3 Correlation Between Clinical Assessment and G Category in 106 Cases of Bladder Carcinoma

	G1	*G2*	*G3*
Flat (7)	1	3	3
Papillary (68)	35	21	12
Invasive i (13)	2	6	5
Invasive ii (16)	1	7	8
Fixed (2)	0	0	2

tissue. In contrast, there is considerable doubt about the wisdom of resecting a large mass just to obtain a deep biopsy; the actual risks from bladder perforation are unknown, but tumour spillage and an inflammatory reaction with adherence of small bowel to the overlying peritoneum seem to be substantial theoretical contraindications. Thus in practice it would seem preferable to continue to make T category a clinical assessment only.

It seems unjustified to place so much emphasis on T2 and T3a tumours when the information will always be so uncertain unless the patient has had a cystectomy. The information that enabled Jewett (1952) to make the distinction between superficial (B1) and deep (B2) invasion was obtained from cystectomy specimens and cannot be obtained from the current therapeutic approaches to these 2 invasive types of tumour.

It was also evident from the present study that a large proportion of tumours apparently invading superficial muscle also had poorly differentiated cell patterns, so that T2 and T3a should almost certainly be merged for the purposes of treatment. A single T2/T3a clinical category would seem advantageous.

All clinical assessments are subject to considerable observer error and it should be expected that bladder tumours would be as prone to this error as any other tumour. Reliance on precise histological diagnosis, staging and grading must remain the most important part of tumour evaluation. The pT category presents few problems for flat and papillary tumours where the pathologist can see the full extent of the tumour. Biopsy and electrode diathermy, the standard treatment for small papillary tumours, may not give the pathologist enough of the base of the tumour for examination and transurethral resection should therefore be encouraged even for these simple tumours.

A further division of P1 tumours has been recommended by Pryor (1973) because in a study of the factors influencing survival of patients with transitional cell tumours, a clear difference was found between those in whom invasion was limited to the core of the papilla (pla) and those where the true lamina propria was invaded (plb).

Serious problems in the use of pT category arise with invasive tumours. Strictly speaking, if all layers of the bladder are not seen, then pTX should be the correct report on invasive tumours. Often a great deal of muscle is available and at least a pT2 category can be determined. We have used the expression pT(+) for some of these tumours invading superficial muscle but a more acceptable method would be for the pathologist to add a descriptive comment, *e.g.* "pT1, muscle was included in the specimen" or "pT2, only superficial muscle included in the specimen". From our experience the clinically invasive "T3" tumours were more often pTX. It was surprising to find that a small proportion of clinically invasive tumours were only pTa or pTl tumours. (The patient with a pTa tumour had an inflammatory mass.)

Thus treatment can never be based on a clinical assessment alone and must always be combined with a "p" category. The accuracy of the stage of those tumours entered into T3 trials must give rise to some concern because while the clinical assessment may be T3, the histopathological category will usually be pTX, though possibly pT2(+). The assessment of these tumours must be based on a resectoscopic biopsy, but efforts to distinguish T2 from T3 by this means are probably unwarranted and unnecessary. Since the biological behaviour of these 2 categories is similar, their treatment should also be similar. It is suggested that a single invasive category (p2/3) may be the most practical classification for these tumours and that future studies should be directed to establishing whether or not this simplification is justified.

It is concluded that despite the recent revision, the TNM classification for bladder cancer is not yet ideal. Although the clinical assessment of any tumour is liable to a large observer error, it is suggested that it is more logical to use the T category as a clinical assessment only and not as a clinicopathological combination.

In practice, both the pathological category and the tumour grade are always used to provide a final classification of a tumour and every effort must be made to ensure adequate tissue for this assessment (indeed, in recognition of the importance of the pathological assessment p might be upgraded to P). Current methods of management of bladder cancer create some difficulty in obtaining an accurate p category but mainly for tumours invading muscle. It is suggested that undue emphasis has been given to determining the extent of the muscle invasion and, since it is so unreliable, invasive tumours should be a single category for both diagnosis and treatment.

One of the purposes of a tumour classification is to correlate the "stage" with prognosis and further consideration should be given to the differences in pl tumours and the use of the subclassification of pl tumours (pla and plb).

The influence on the prognosis of *in situ* changes in the prostatic urethra, elsewhere in the bladder and in the ureter might also be considered in future amendments to the TNM classification.

Appendix: TNM for Bladder Cancer, UICC (1978)

Rules for Classification

The classification applies only to epithelial tumours. Papilloma is excluded but such cases should be listed under the category "GO". Papillary non-invasive carcinoma should be listed under the category Ta.

There should be histological or cytological verification of the disease. Any unconfirmed cases must be reported separately.

The following are the minimum requirements for assessment of the T, N and M categories. If these cannot be met the symbol TX, NX or MX will be used.

T categories:	Clinical examination, urography, cystoscopy, bimanual examination under anaesthesia and biopsy or transurethral resection of the tumour (if indicated) prior to definitive treatment.
N categories:	Clinical examination and radiography including lymphography and urography.
M categories:	Clinical examination and radiography. In the more advanced primary tumours or when clinical suspicion warrants, radiographic or isotope studies are recommended.

Regional and Juxta-regional Lymph Nodes

The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries.

The juxta-regional lymph nodes are the inguinal nodes, the common iliac nodes and the para-aortic nodes.

TNM Pre-treatment Clinical Classification

T—Primary

Tis	Pre-invasive carcinoma (carcinoma *in situ*): "Flat tumour".
Ta	Papillary non-invasive carcinoma.
T0	No evidence of primary tumour.
T1	On bimanual examination a freely mobile mass may be felt: this should not be felt after complete transurethral resection of the lesion and/or Microscopically, the tumour does not invade beyond the lamina propria.
T2	On bimanual examination there is induration of the bladder wall which is mobile. There is no residual induration after complete transurethral resection of the lesion and/or There is microscopic invasion of superficial muscle.
T3	On bimanual examination induration or a nodular mobile mass is palpable in the bladder wall which persists after transurethral resection of the exophytic portion of the lesion and/or There is microscopic invasion of deep muscle or extension through the bladder wall. T3a Invasion of deep muscle. T3b Invasion through the bladder wall.
T4	Tumour fixed or extending to neighbouring structures and/or There is microscopic evidence of such involvement. T4a Tumour infiltrating the prostate, uterus or vagina. T4b Tumour fixed to the pelvic wall and/or abdominal wall.
TX	The minimum requirements to assess the primary tumour cannot be met.

N—Regional and Juxta-regional Lymph Nodes

N0	No evidence of regional node involvement.
N1	Evidence of involvement of a single homolateral regional lymph node.
N2	Evidence of involvement of contralateral or bilateral or multiple regional lymph nodes.
N3	Evidence of involvement of fixed regional lymph nodes (there is a fixed mass on the pelvic wall with a free space between this and the tumour).
N4	Evidence of involvement of juxta-regional lymph nodes.
NX	The minimum requirements to assess the regional and/or juxta-regional lymph nodes cannot be met.

M—Distant Metastases

M0	No evidence of distant metastases.
M1	Evidence of distant metastases.
MX	The minimum requirements to assess the presence of distant metastases cannot be met.

p.TNM Post-surgical Histopathological Classification

pT—Primary Tumour

pTis Pre-invasive carcinoma (carcinoma *in situ*).

pTa Papillary non-invasive carcinoma.
pT0 No evidence of tumour found on histological examination of specimen.
pT1 Tumour not extending beyond the lamina propria.
pT2 Tumour with invasion of superficial muscle (not more than half-way through muscle coat).
pT3 Tumour with invasion of deep muscle (more than half-way through muscle coat) or with invasion of perivesical tissue.
pT4 Tumour with invasion of prostate or other extra-vesical structures.
pTX The extent of invasion cannot be assessed.

G—Histopathological Grading

"G0" Papilloma—*i.e.* no evidence of anaplasia.
G1 High degree of differentiation.
G2 Medium degree of differentiation.
G3 Low degree of differentiation or undifferentiated.
GX Grade cannot be assessed.

L—Invasion of Lymphatics

L0 No lymphatic invasion.
L1 Evidence of invasion of superficial lymphatics.
L2 Evidence of invasion of deep lymphatics.
LX Lymphatic invasion cannot be assessed.

pN—Regional and Juxta-regional Lymph Nodes

The pN categories correspond to the N categories.

pM—Distant Metastases

The pM categories correspond to the M categories.

Stage Grouping

No stage-grouping is at present recommended.

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T3 Bladder Cancer—the Case for Salvage Cystectomy

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Summary—Seven hundred and four patients with bladder cancer treated by radiotherapy at the London Hospital between 1965 and 1974 have been followed for a minimum period of 5 years. Invasive tumours were usually treated by radical radiotherapy. Cystectomy was reserved for patients whose tumours did not respond to radiation, recurred later on, or who developed complications from radiotherapy.

The crude 5-year survival rate for T3 tumours in this series was 38%—similar to that obtained in other centres using pre-operative radiation followed by cystectomy, but this overall figure conceals the important difference between 2 distinct tumour populations. Nearly half of these tumours appear to be radiosensitive, giving a 56% crude 5-year survival rate for T3 tumours. The remainder are radioinsensitive, with only a 17% crude 5-year survival rate for T3 tumours. When there is a good initial response to radiotherapy there would seem to be no necessity to insist upon cystectomy.

Cystectomy or radiotherapy alone are known to give poor results in the treatment of invasive tumours of the bladder, and for some time it has been accepted that a pre-operative course of radiotherapy ought to be followed by total cystectomy for T3 bladder tumours. At the London Hospital for the last 16 years we have in general followed a policy of offering the patient a radical course of radiotherapy in the hope that it might cure the disease. We have reserved cystectomy for those patients in whom the growth did not regress, who developed serious complications after the radiotherapy, or in whom a recurrence developed in the course of follow-up. This study reports this experience from a single centre, followed up for a minimum of 5 years.

Patients and Methods

Seven hundred and forty-eight patients referred to the London Hospital from 1965 to 1974 were studied. Of these, 21 were unfit for any treatment other than palliation and 23 had received some other form of surgical treatment at another centre prior to being referred here and are excluded from this series.

All patients were evaluated by means of deep biopsies at cystoscopy and by bimanual palpation, intravenous urography, blood count, urea and electrolyte estimation and chest radiograph. They were staged according to the TNM system, with the exception that lymphography was rarely used (Table 1). It will be noted that 37% were already in T4 category.

Table 1 Radiotherapy and Bladder Cancer—Patients by Stage

Stage	*No.*	*%*
T1	90	13
T2	132	19
T3	220	31
T4	262	37
Total	704	100

This series included patients of all ages (Table 2):

Table 2 Radiotherapy and Bladder Cancer—Stage and Age

	<55	*55-64*	*65-74*	*75-91*
T1	28	28	24	10
T2	18	46	40	28
T3	29	68	84	39
T4	29	75	98	60
Total	104	207	246	137
%	15	31	35	19 (av. 68)

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 3 Radiotherapy and Bladder Cancer—Tumour Stage and Dosage

	<5000	*5-5500*	*6000*
T1	16	65	3
T2	22	87	16
T3	57	129	32
T4	177	58	10
Total	272	339	61
%	40	50	10

8% had salvage cystectomy.

55% of these patients were over the age of 65, and the mean age of the series was 68 years.

Technique of Radiotherapy

During the period of this review it was the policy to offer patients, when possible, a standard method of treatment which aimed to treat the bladder and a 1 to 2 cm margin around, to a standard tumour dose of 5000 to 5500 R in 20 daily fractions 5 days per week with Co^{60}. The tumour was localised with a cystogram and skin marks using AP, PA and lateral radiographs. A 3-field pin-and-arc technique was used. A fixed head Telecobalt unit with a Johns collimator was employed. Although this was the standard method aimed at (Table 3), many patients received less than this dose, either because their tumours were far advanced and the aim of therapy was palliative, or because the patients were too ill for a more radical course of treatment. Some patients received a larger dose with a wider field, when we were participating in multicentre clinical trials. (Since this series was compiled, the technique used in our centre has altered with the advent of the linear accelerator.)

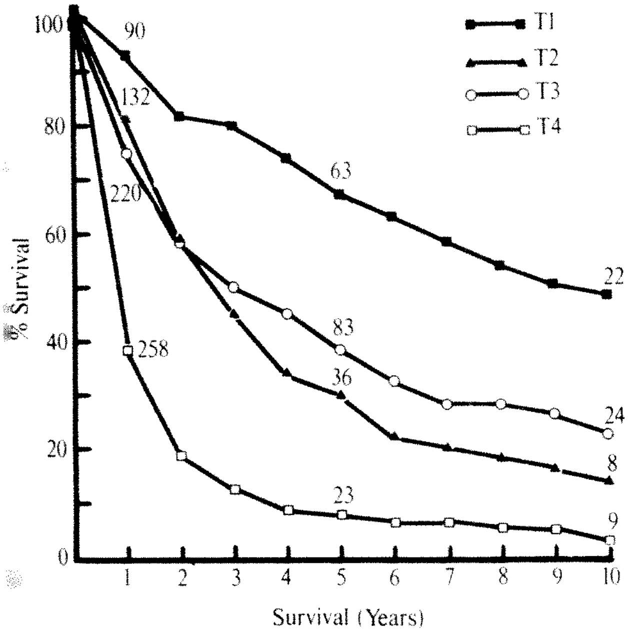

Fig. 1 Actuarial survival of all patients according to T stage at time of radiotherapy treatment.

Table 4 Radiotherapy and Bladder Cancer—5-year Survival by Stage

Stage	*No.*	*Survived*	*%*	
T1	90	63	70	
T2	132	36	27	34
T3	220	83	38	
T4	262	24	9	
Total	704	206	29	

Follow-up

All patients were followed by regular cystoscopy and bimanual examination with biopsies when indicated. All patients have been followed for a minimum of 5 years, or until death.

Response to Treatment

Although tumours that were going to regress completely usually showed marked improvement at the first cystoscopy 3 months after the completion of treatment, some continued to improve. For the purposes of analysis of this series we have chosen the cystoscopic appearance at 6 months as the index of "complete" or "partial" response of the tumour.

Results

The results for the 704 patients are shown in Figure 1, which is a computer-based actuarial analysis of the follow-up data. The crude survival data are given in Table 4. These data must, at first glance, seem suspect, since they seem to show a better survival in the T3 group than in the T2 group. Since the assessment of the T category depends upon the observer's interpretation of the findings at bimanual examination under anaesthesia, together with the evidence in the histological section of muscular invasion, there is much room for observer error. We have therefore

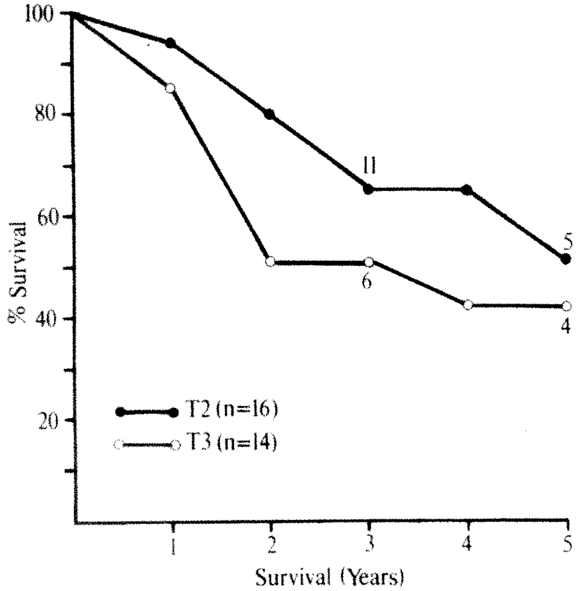

Fig. 2 Survival of patients with Grade 2 tumour according to pre-radiotherapy T stage (personal series H.R.E.).

examined a smaller number of patients who were all evaluated by one observer (H.R.E.): 89 of these were placed in categories T2 or T3. Figure 2 shows that the actuarial survival rate for the more superficial tumours was better than those in T3 provided the tumour grade was of intermediate malignancy (G2), but that in the anaplastic group (G3) the survival curves are almost identical (Fig. 3).

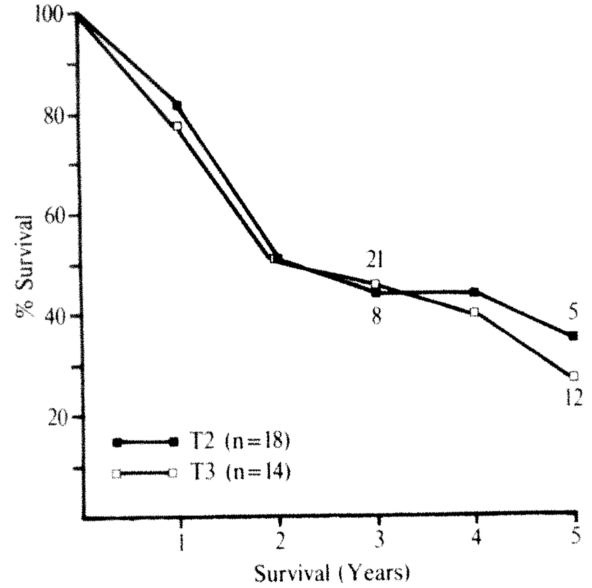

Fig. 3 Survival of patients with Grade 3 tumour according to pre-radiotherapy T stage (personal series H.R.E.).

Table 5 Radiotherapy and Bladder Cancer—Influence of Age on Survivals at 5 Years: T2 and T3 tumours

Age	*No.*	*Surv.*	*5-year surv. (%)*
<55	47	27	57
55-64	114	45	39
65-74	124	39	31
75-91	67	8	12
All cases	352	149	34

Age and Survival (Table 5)

Inevitably, older patients lived less long, but it is important to note in this series that the 5-year crude survival rate of 57% for patients under 55 years of age does not suggest that by with-holding cystectomy from them, our policy of treatment was depriving these patients of any therapeutic advantage.

Tumour Response and Stage (Table 6)

With the exception of patients who presented for treatment with fixed inoperable cancers in T4 category, there was a complete regression of tumour after radiotherapy in 42 to 49% of patients. The more superficial the tumour, the greater the proportion showing good response. In particular, 42% of T3 patients responded completely.

Survival of T3 Tumours

The most striking feature to emerge from this analysis has been the difference in survival of those patients with deeply infiltrating T3 tumours who showed an initial complete response from those who did not. Figure 4 is calculated on an actuarial basis and may give too optimistic a view of the survival pattern for the responders; nevertheless, the crude survival rates still show an impressive difference (Table 7).

Table 6 Radiotherapy and Bladder Cancer—Response by Stage

Stage	*Complete*	*>50%*	*<50%*
T1	49%	22%	29%
T2	48	26	26
T3	42	25	33
T4	6	30	64

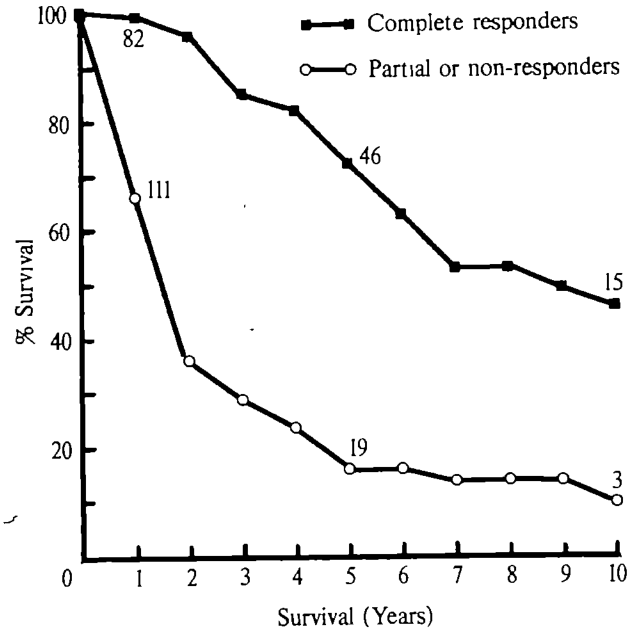

Fig. 4 Actuarial survival of T3 patients according to response to treatment.

The Place of Total Cystectomy

During the period of review (1965-74) a salvage cystectomy was performed in only 8% of the patients; in these patients the operative mortality was high, and at 3 months after cystectomy had risen to 22%. Many of these patients underwent cystectomy for intolerable symptoms and their age range exceeded the customary limits for the indications for this formidable operation. With recent improvements in post-operative management and, in particular, with parenteral hyperalimentation, the operative mortality has fallen (Table 8).

When we studied the effect of cystectomy in this series (Fig. 5), it was apparent that when it was feasible, and the patient's general condition permitted cystectomy after failure of radiotherapy to produce an initial complete response, then cystectomy was followed by a marked improvement in the survival rate. Equally, in those patients whose tumours had initially shown a complete response to radiotherapy, when total cystectomy was needed later on for recurrence of disease in the bladder or for intolerable side effects from radiation (and this was needed in only 2 patients), whatever the benefit to the patient in terms of relief of symptoms, we could see no improvement in overall survival. Many factors contributed to the decision to advise cystectomy in each patient, and it would be incorrect to draw the conclusion from these data that cystectomy is useless or contraindicated in patients who initially show a complete response to radiotherapy. If we limit the consideration of the role of salvage cystectomy to those initially placed in the category T3 (Fig. 6), again there is a marked improvement in survival of those patients whose tumours did not at first respond to radiation and who were judged fit to undergo cystectomy.

Table 7 Radiotherapy and Bladder Cancer—Survival at 5 Years by Response to Radiotherapy

When no residual tumour at 6 months	65% (all stages)
When residual tumour	14% (all stages)
($P < 0.001$)	
For T3 category only	56% v. 17%

Table 8 Mortality 3 Months After Total Cystectomy: 1965-80

		No.	*Mortality (%)*
Elective cystectomy after pre-operative RT	1965-1975	18	17
Salvage cystectomy	1965-1975	58	22
Salvage cystectomy	1977-1980	18	11

Discussion

The overall results of the method of treatment used in this series are very similar to those reported

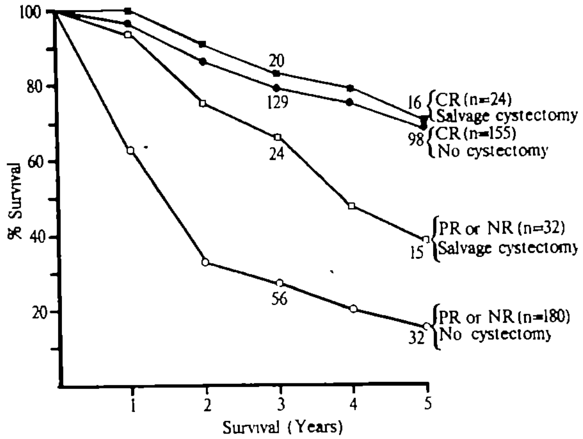

Fig. 5 Influence of salvage cystectomy on survival in complete responder (CR) v. partial responder (PR) or non-responder (NR) patients after radiotherapy (all stages).

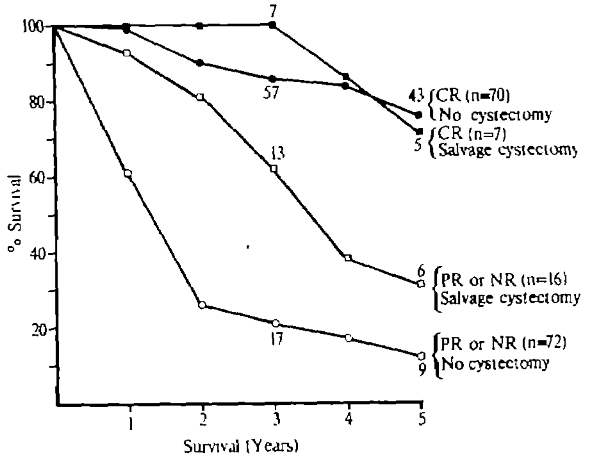

Fig. 6 Influence of salvage cystectomy on survival in complete responder (CR) v. partial responder (PR) or non-responder (NR) patients after radiotherapy (T3 cases only).

by other observers using different combinations of radiotherapy and cystectomy. What is, we think, of some interest, is the suggestion from these data that there may be 2 tumour populations, one radiosensitive and the other radioresistant, and that a good survival rate is to be found in the patients whose tumours show a marked initial response to radiotherapy. Our figures closely echo the findings in the collaborative survey reported by Wallace and Bloom (1976). It will be recalled that they reported a 51% 5-year survival rate in the T3 tumours in which a reduction in stage was found at cystectomy, compared with a 22% survival rate in those patients not showing any stage reduction.

The lesson to be drawn is that cystectomy may very reasonably be with-held in the initial treatment of the patient with invasive bladder cancer, and that a radical course of radiotherapy, using the small field used in this series, should be given first. If the tumour then responds completely, or if there is a partial response at 3 months—then the decision may be deferred for 6 months; then, if there has been complete regression of the tumour, the patient need only be followed up carefully. If, by this time, the tumour has not completely regressed, then cystectomy should be performed when the patient is fit for it. Our data suggest that a patient loses nothing by trying radiotherapy first. One can expect a complete response in nearly half of the T2 and T3 patients, and most of those who do respond will be enabled to live out their allotted years without the discomfort and dangers of total cystectomy. For those who do not respond, then salvage cystectomy is well worthwhile.

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The Management of Squamous Cell Carcinoma of the Bladder

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Summary—Fifty-one patients with pure squamous cell carcinoma of the bladder were treated between 1958 and 1978. The overall 5-year survival rate was 16%. Ninety-two per cent of cancer deaths were caused by failure to control local disease; treatment by radiotherapy and elective cystectomy resulted in no long-term survivors. It is concluded that earlier diagnosis would reduce the number of cases presenting with advanced local disease and that future research should be directed towards adjuvant studies with chemotherapeutic agents known to have activity against bladder cancer.

Primary squamous cell carcinoma of the bladder is uncommon, accounting for only 3 to 6.7% of all bladder tumours (Johnson *et al.*, 1976). It is generally associated with a poor prognosis and a poor response to radiotherapy. Wallace (1976) commented that survivors were few, and that of these all had been treated by extirpative surgery. Only 24 cases were reported in the Bristol Bladder Tumour Registry (Miller *et al.*, 1969) and all of these patients died of progressive disease.

A review was undertaken of patients treated between 1958 and 1978 at the Royal Marsden Hospital to try and identify factors in the aetiology, presentation and treatment of this disease which affected the prognosis.

Patients and Methods

Between 1958 and 1978, 120 cases of squamous cell carcinoma of the bladder were recorded in the Cancer Registry. A histopathological review of available histological material was undertaken and only cases which showed keratinisation of a large part of the tumour were included.

Fifty-one patients were found to fulfil this criterion. There were 33 men and 18 women (male:female ratio was 1.8:1). Their mean age was 63 years (range 35-94 years), and their survival ranged from 1 week to 16 years.

Results

Table 1 Analysis of Possible Aetiological Factors

Smoking	Men	15/33	(45%)
	Women	1/18	(5%)
	Total	16/51	(31%)
Bilharzia	Men	2/33	(6%)
Urethral stricture	Men	3/33	(9%)
	Women	1/18	(5%)
	Total	4/51	(8%)
Bladder stone	Men	3/33	(9%)
Chronic urinary infection	Women	1/18	(5%)
Industrial exposure	Men	1/33	(3%)
Neuropathic bladder		0	
Leukoplakia		0	

An analysis of aetiological factors commonly thought to be associated with this disease is shown in Table 1. There were only 2 cases of bilharzia and although 31% of the patients had urinary tract infections at presentation, half of these had undergone instrumentation prior to referral. All of the patients with stones and urethral strictures had urinary infections, but only one female patient had a history of chronic urinary infection unassociated with stones or stricture. No cases of longstanding leukoplakia or neuropathic bladder were encountered.

The 3, 5 and 10 year survival figures are shown in Table 2. All the patients who survived to 3

Table 2 Crude Survival

	3 years	*5 years*	*10 years*
Men	7 (21%)	7	4
Women	1 (5%)	1	0
Total	8 (16%)	8	4 (8%)

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

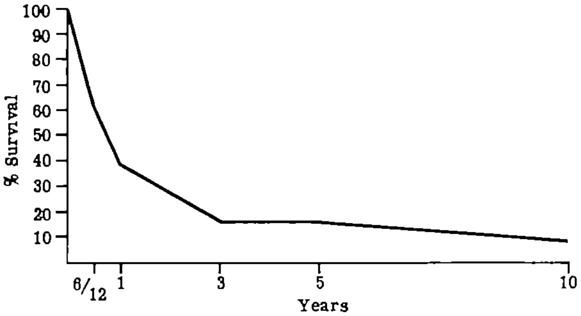

Fig. 1 Survival curve: all cases.

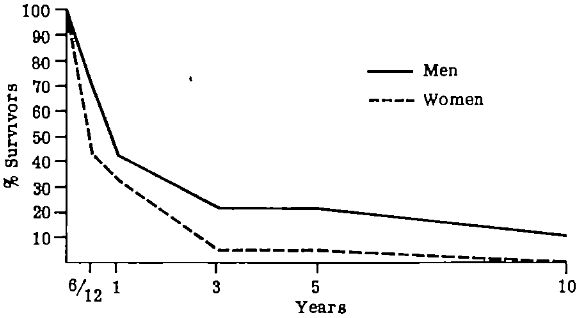

Fig. 2 Survival curves: comparison of males and females

years were alive at 5 years. The survival curves (Figs. 1 and 2) show a sharp fall in survival during the first 3 years and thereafter the curve flattened out. Males and females showed a similar pattern.

The survival of patients related to the duration of their symptoms is shown in Table 3. More than half the patients had experienced symptoms for more than 3 months. The 3-year survival of patients whose symptoms had been present for less than 3 months was twice that of patients with longer histories. Only 9 patients had received previous therapy, other than endoscopic biopsy (Table 4).

The T category of all patients is shown in Table 5. There were only 2 superficially invasive tumours and no non-invasive tumours. Six cases which could not be staged all had deeply infiltrating advanced tumours and had been accepted for palliative radiotherapy at the Royal Marsden Hospital. The 5-year survival rate of T3 tumours was 26% and there was a 10% 5-year survival for T4 tumours.

Table 3 Survival Compared to Duration of Symptoms

Survival	*Duration of symptoms*		
	<3/12	*3-6/12*	*>6/12*
<1 year (37 patients)	14	11	12
1-3 years (6 patients)	2	3	1
3 years + (8 patients)	5	2	1
Total	21	16	14

Symptoms <3/12—3 year survival = 24%.
Symptoms >3/12—3 year survival = 10%.

Table 4 Survival Related to Previous Therapy

<1 year (37 patients)	Diathermy	1
	Partial cystectomy	2
	Laparotomy	1
	Radiotherapy	1
		5
1-3 years (6 patients)	Partial cystectomy	2
	Open biopsy	1
		3
3 years + (8 patients)	Partial cystectomy	1

Only 8% of patients developed distant metastases and one of these with liver secondaries also had a primary bronchial tumour (Table 6). The methods of treatment are shown in Table 7. Thirteen patients were commenced on a course of radiotherapy but died before completing treatment. They were all advanced T4 or Tx cases and represented a group of patients who presented with hopelessly advanced disease. Of the cases that completed radiotherapy, 36% survived for 5 years and one had undergone a salvage cystectomy. A second patient who had a salvage cystectomy died in the post-operative period. Of 7 patients who were treated with pre-operative radiotherapy and elective cystectomy, none survived beyond one year. There were 2 post-operative deaths in this group.

The causes of death are shown in Table 8. Only 2 patients died of unrelated disease, although the autopsy rate was only 14%. Two of the post-operative deaths were found to have residual pelvic disease at autopsy.

Table 5 Survival Compared to T Stage

T stage	*Survival*			
	1 year	*1-3 years*	*3 years+*	*Total*
T1	—	—	—	0
T2	2	—	—	2
T3	12	5	6	23
T4	17	1	2	20
Tx	6	0	0	6

Table 6 Distant Metastases (Number of Deaths from Metastatic Disease = 4/51 (8%))

Survival of patients with metastases		
<1 year	*1-3 years*	*3 years+*
2—bone	2—1 distant nodes 1 liver (also had Ng. bronchus)	Nil

Discussion

Our series of 51 patients confirms the higher incidence of squamous cell cancer in females compared to transitional cell tumours which has been noted by other authors (Johnson *et al.*, 1976; Richie *et al.*, 1976). This observation, and the association of squamous cell tumours with leukoplakia (O'Flynn and Mullaney, 1967, 1974; Morgan and Cameron, 1980) have led to speculation that this higher incidence of squamous metaplasia in the female bladder, in conjunction with infection and stone formation, is a prime factor in the aetiology of this disease (Sakkas, 1966). However, although one-third of our cases had urinary infection at the time of presentation, only one of our patients had a proven history of chronic urinary infection. In our series there were no cases of longstanding leukoplakia or neuropathic bladder.

The worsening of the prognosis of bladder cancer occasioned by delay in diagnosis has been well established (Wallace and Harris, 1965). This has been confirmed in this series and probably accounts for the high mortality rate in the first year. Few of the patients had received previous treatment and inadequate therapy did not seem to be a factor affecting survival. It is to be hoped that better early diagnostic facilities and the careful follow-up of patients with chronic urinary infection and bladder stones will reduce the number of patients presenting with hopelessly advanced disease.

Table 7 Survival According to Initial Therapy

Years	*<1*	*1-3*	*3*	*5*	*10*
Radical radiotherapy	9	6	7	7	3
Radical radiotherapy + salvage cystectomy	1	—	1	1	1
Radiotherapy + elective cystectomy	7	—	—	—	—
Interstitial implant	1	—	—	—	—
Cystectomy alone	2	—	—	—	—
Radiotherapy + partial cystectomy	1	—	—	—	—
Palliative radiotherapy	3	—	—	—	—
Failed to complete radiotherapy	13	—	—	—	—

Table 8 Causes of Death

	Survival (years)				
	<1	*1-3*	*3*	*5*	*10*
Bladder cancer	36	4	0	0	0
Operative mortality	3*	—	—	—	—
Unrelated disease	0	2	—	—	—
Autopsy performed	5	2	—	—	—

* Two residual cancer.

The 5-year survival rate for T3 cases of 26% dispels some of the gloomy views of this disease which have been expressed in the past. However, compared to some recent series, none of our long-term survivors was treated by radiotherapy and elective cystectomy. Richie *et al.* (1976) reported a 5-year survival rate of 50% for stage B2 and C tumours. All of their cases underwent radical cystectomy, and one-third received pre-operative radiotherapy. Johnson *et al.* (1976) reported a 5-year survival rate of 34% in stage B2 and C tumours with combined treatment compared to a 17.7% rate for radical radiotherapy alone. This did not achieve statistical significance at 5 years. Our findings are also at variance with the results of the Institute of Urology trial on mainly transitional cell disease, which showed increased survival with radiotherapy and elective cystectomy (Wallace and Bloom, 1976), although again, not of statistical significance. Clearly, only a controlled clinical trial would resolve these contradictions, and with the comparative rarity of this disease, such a trial would take many years to complete, even with multicentre participation.

Although the majority of our patients died of bladder cancer, only 8% developed distant metastases. Thus, the majority of our patients died as a result of failure to control their local disease. Although extending the radiotherapy field to para-aortic nodes might improve local control, this would probably be associated with a higher morbidity and possibly make salvage surgery more hazardous. It is suggested that future research be directed towards adjuvant chemotherapeutic studies with agents known to possess activity against bladder cancer, in the hope of controlling small volume metastases which may be undetectable outside conventional radiotherapy fields.

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Ileal Conduit Urinary Diversion: Long-term Follow-up in Adults

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Summary—Ninety-six adult patients who had an ileal conduit urinary diversion between 1970 and 1976 were reviewed. Forty-nine of the patients had been followed up for an average period of 6 years. In this group, the upper tracts showed an improvement in 23%, whilst deterioration, which could be attributable to the conduit, occurred in 16%. Late complications included stomal problems in 9 patients, pyelonephritis in 2 and renal calculi in 3. Eight out of 9 patients examined had a reduced glomerular filtration rate as calculated from Tc DTPA clearance.

Recent long-term studies of ileal conduit urinary diversion have shown that there is a high incidence of late complications with progressive deterioration of the upper renal tracts, pyelonephritis, calculi formation and stomal problems. In children the incidence of late complications is as high as 80% (Dunn *et al.*, 1979). We report a retrospective review of our experience of ileal conduits in adults.

Patients and Methods

Ninety-six patients who had an ileal conduit diversion between 1970 and 1976 were reviewed. The patients were divided into 2 groups—a malignant group of 71 patients (50 males, 21 females) with an age range of 31 to 80 years (average 61.4 years) and a non-malignant group of 25 (9 males, 16 females) whose ages ranged from 16 to 67 years (average 40.6 years).

Indications for Diversion

In the malignant group 67 patients required diversion following cystectomy for carcinoma of the bladder. The majority of these tumours were deeply invasive, with 67% having had radical radiotherapy before operation. The remaining 4 patients had a palliative diversion for advanced carcinoma of the cervix with a vesicovaginal fistula.

In the non-malignant group the commonest indication for diversion was a neurogenic bladder (Table 1). Of the sacral tumours one was a lipoma of the cauda equina and the other an osteoclastoma previously treated by radiotherapy and which has shown no evidence of recurrence.

Mortality

There were no post-operative deaths in the non-malignant group but 3 of the 25 patients have died subsequently. One patient was a diabetic who succumbed to ketoacidosis. The other 2 patients died from carcinoma of the colon and a drug overdose, respectively.

Table 1 Indications for Operation in the Non-Malignant Group

Neurogenic bladder—12 cases	
Sacral tumour	2
Sacral agenesis	2
Diabetic neuropathy	2
Disseminated sclerosis	2
LMN disease	1
Myelomeningocoele	1
Post-hysterectomy	1
Idiopathic	1
Ectopia vesicae—4 cases (1—adenocarcinoma)	
Interstitial cystitis—3 cases	
Small capacity bladder—4 cases	
Tuberculous	1
Non-tuberculous	2
Post-radiotherapy	1
Epispadias—1 case	
Incontinence—1 case	

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Mortality in the Malignant Group—71 Patients

Post-operative	9
Recurrence—carcinoma of bladder	35
—carcinoma of cervix	4
Intestinal obstruction	2
Pulmonary embolus	1
Further carcinoma (penis 1, bronchus 1)	2
Renal failure	1
Overall mortality 54 (76%)	

There were 9 post-operative deaths (12.5%) in the malignant group associated with the more extensive surgery and radiotherapy. The patients in this group were older and less fit. Of the 62 remaining patients there have been 45 late deaths, the majority from recurrence of their malignancy (Table 2). The overall mortality was 76%.

The death of only one patient can be attributed directly to the urinary diversion. She was a lady who developed bilateral staghorn calculi with deteriorating renal function. She refused further treatment and eventually died about 9 years following cystectomy and diversion. There was no evidence of recurrent tumour.

Two patients developed new primary carcinomas (penis and bronchus) from which they eventually died.

Operation

The stoma site was carefully selected and marked before operation in consultation with the stoma care nurse. It was usually sited in the right iliac fossa unless previous operation scars were present, when the left side was used. The stomal incision, with excision of skin and external oblique fascia, was made before the main laparotomy incision.

In most cases a 20 cm length of terminal ileum was isolated for the conduit. A more proximal part of ileum was used if the patient had previously had radiotherapy.

The first 76 patients had a ureteroileal anastomosis carried out by the Wallace I technique (Wallace, 1966). Wallace (1970) modified this technique to avoid possible kinking of the ureters and this modification was used in 14 patients. Six patients had a single ureter. The ureters were usually drained by 8 FG infant feeding tubes brought out through the stoma during the post-operative period. Kinking of the ureters has not been a problem.

When present, the appendix was removed in all patients.

Results

Early Complications (Table 3)

Early complications occurred most frequently in the malignant group.

Wound infection was the most common problem. In the malignant group transverse and vertical incisions were both equally prone to infection and in nearly all cases the patient had had radiotherapy before operation. Incisional hernia developed later in 2 of these infected wounds.

Urinary leakage from the ureteroileal anastomosis was not a common problem. In each case it settled with conservative management.

Pelvic infection, septicaemia, bleeding and pulmonary embolism were problems related to the more extensive procedure of cystectomy rather than to the urinary diversion alone.

Infarction of the conduit occurred in one case.

Late Complications (Table 4)

Stomal problems have been relatively few. There were 5 parastomal herniae, 3 of which have required repair. One was repaired as an emergency because of obstruction of the conduit. Five cases of stomal retraction have occurred, all in the non-malignant group, and 2 of these required re-fashioning. One of these also had stomal stenosis.

Skin soreness seemed to be a relatively common problem, but this included any patient who had any skin trouble, however slight. With improved urostomy appliances and skilled management by

Table 3 Early Complications

	Malignant (71 cases)	*Non-malignant (25 cases)*
Wound infection	16 (22%)	5 (20%)
Wound dehiscence	1 (1.5%)	—
Urinary leakage	2 (3%)	3 (12%)
Prolonged ileus	11 (15%)	2 (8%)
Pulmonary embolus	5 (7%)	—
Haemorrhage	3 (4%)	—
Septicaemia	4 (6%)	—
Pelvic abscess	3 (4%)	—
Cerebrovascular accident	1 (1.5%)	—
Small bowel obstruction	1 (1.5%)	—
Conduit infarctions	1 (1.5%)	—

Table 4 Late Complications

	Malignant (52 cases)	*Non-malignant (24 cases)*
Incisional hernia	2 (4%)	—
Parastomal hernia	3 (6%)	2 (8%)
Stomal prolapse	3 (6%)	—
Stomal retraction	—	5 (21%)
Stomal stenosis	—	1 (4%)
Skin soreness	14 (27%)	11 (46%)
Diarrhoea	3 (6%)	3 (12%)
Pyocystis	—	5 (21%)
Haematuria	3 (6%) (1 tumour)	2 (8%)
Renal stones	2 (4%)	1 (4%)

the stoma care nurse, this problem has become less frequent.

Six patients had persistent diarrhoea following diversion. Exclusion of a short length of ileum should not produce a "short gut" syndrome, nor should the bowel bacterial flora be altered significantly, but absorption of conjugated bile acids will be reduced.

Pyocystis occurred in 5 cases in the non-malignant group but Hibitane bladder washouts were sufficient to control the condition in all cases.

Recurrent attacks of haematuria occurred in 5 patients; a definite cause was found in only one, due to a papillary tumour in the renal pelvis.

Renal calculi occurred in 3 patients. Two patients developed staghorn calculi, whilst the third passed his stone spontaneously via the conduit; he has not formed further calculi.

A persistently low bicarbonate was not a common problem, but 2 patients have had repeated episodes of electrolyte disturbance and acidosis. One patient was a diabetic and the other patient formed bilateral staghorn calculi with progressive renal failure. They both ultimately died during an episode of severe metabolic imbalance.

Follow-up

Progress has been assessed by the excretory urogram, bacteriological examination of the urine and, in a few cases, by isotope renography.

Excretory Urogram

Excretory urograms were carried out at 3 months, 1 year and then at approximately 2-yearly intervals after operation. Twenty patients were excluded from further assessment as they all died within 6 months of operation.

The remaining patients were further subdivided into short-term follow-up (27 patients—all but one being in the malignant group) who died from 6 months to 3 years following diversion, and long-term follow-up (49 patients of whom 26 were from the malignant group) who survived 3 years or longer. The average length of long-term follow-up was 6 years.

Short-term Follow-up

The excretory urogram showed improvement in 9 patients (33%), no change in 13 (48%) and 5 (19%) showed deterioration of the upper tracts. In at least 3 of the latter 5 patients deterioration was caused by recurrent tumour obstructing one or both ureters.

Long-term Follow-up

Five patients were excluded from this group as they had not had excretory urograms for several years for various reasons. The majority of patients have had urography within the last year.

The excretory urogram in 10 patients (23%) has shown improvement; there was no change in 24 (54%) and deterioration in the remaining 10 (23%). Of the 10 patients who showed deterioration 3 were due to tumour causing ureteric obstruction. Two formed renal calculi, one showed pyelonephritic scarring and one ileal conduit obstruction due to a parastomal hernia. There was non-obstructed dilatation of the upper tracts in the remaining 3 patients, the dilatation being slight in 2 but in the third there was marked progressive dilatation over several years. However, all 3 patients remain well at the present time. One other patient passed a stone via the conduit but there was no alteration in his excretory urogram.

Urine Infection

During follow-up, ileal conduit urine specimens were not routinely cultured unless there was a clinical indication. For the purpose of this review a catheter specimen of urine was taken from the conduit for culture in 34 patients. In 20 the urine was sterile and in the remaining 14 (41%) there was a significant growth: *Esch. coli* was cultured in 11, *Proteus* in 2 and *Ps. pyocyanea* in 1.

Excretory urograms in 6 of the 34 patients showed upper tract deterioration and 4 of these had infected urine. The numbers are not sufficient to draw any conclusions as to the relationship between urinary infection and upper tract deterioration. One patient out of the 34 who had renal calculi had infected urine (*Ps. pyocyanea*) with pyuria.

Isotope Renograms

Radioisotope renography has been carried out on several patients to investigate the possibility of obtaining a more accurate assessment of the renal tracts following diversion. Nine patients have had a technetium 99^m—DTPA gamma camera renogram performed with a diuretic given at 15 min. The glomerular filtration rate (GFR) as calculated from the rate of clearance of the DTPA given for the gamma camera renogram was low in 8 of the 9 patients, ranging from 11 to 60 ml/min (average 38 ml/min). Only one of these patients' excretory urogram had shown deterioration with slight dilatation of the upper tracts.

None of the upper tracts showed an obstructed pattern on renography but stasis was demonstrated in 3 of the kidneys. There has not been any sign of deterioration on urography in these 3 kidneys.

Discussion

The crude overall mortality has been high—57 deaths out of 96 patients (59.4%), with 47 (49%) dying in the first 3 years. This is hardly surprising since a large proportion of the patients had advanced malignant disease. Thus the numbers that could be followed up on a long-term basis were severely limited.

The reported progressive deterioration of the upper tracts in several adult series has ranged from 14 to 28%—several of these series having an average follow-up of less than 4 years (Murphy and Schoenberg, 1967; Schmidt *et al.*, 1973; Pitts and Muecke, 1979). In this series 23% of upper tracts have shown deterioration in the long term. If those patients with upper tract dilatation due to recurrent tumour and not due to the conduit are excluded, this figure is reduced to 16%.

Tc DTPA clearance measurements showed that in all patients except one the glomerular filtration rate was reduced. Renal function therefore seemed to be diminished in these patients, but because GFR was not measured before diversion one cannot comment on whether renal function had deteriorated. However, there were 6 patients with an estimated low GFR and normal urograms both before and since diversion who give cause for concern. Their renal function may well have diminished since diversion and if it continues to deteriorate, then presumably changes will be seen on urography. Excretory urography is a poor test of renal function.

The reported incidence of pyelonephritis has been very variable. Schmidt *et al.* (1973) reported an incidence of acute pyelonephritis of 21.9%, In our series one patient developed scarring on excretory urography and another had recurrent attacks of acute pyelonephritis. Fresh scarring did not develop on her urogram.

Although 41% of our surviving patients had infected urine, the incidence of pyelonephritis was low and infection did not seem to be a factor in the development of pyelonephritis. This was further supported by the fact that the one patient who developed pyelonephritic scarring on urography had sterile urine. In 10 of the 14 patients who had an infected urine, there was no deterioration of the upper tracts on urography.

The incidence of late complications in this series has been low. The occurrence of stomal problems varies widely in published series. It is mainly a problem in children, with an incidence as high as 50% (Dunn *et al.*, 1979). Murphy and Schoenberg (1967) have reported an incidence of stomal stenosis in 20.4% of their patients, but we have had only one case. Stomal retraction (5 cases) has occurred only in the non-malignant group; the reason for this is not obvious. Nine patients (12%) have had one or more stomal problems and 5 of these have required surgical correction. The remaining 4 patients have been treated conservatively by skilled management of the stoma and correct choice of urostomy appliance. Skin problems have occurred frequently and once again management has been along the same lines. We believe it is essential to have an experienced stoma care nurse who has an extensive knowledge not only of stomal and skin problems but also of the available urostomy appliances. The incidence and morbidity of these problems have decreased since being managed by a stoma care nurse.

We have not had any problems with uretero-ileal stenosis, whereas in other series this has been a significant complication (Burnham and Farrer, 1960; Schmidt *et al.*, 1973).

The incidence of renal calculi in other adult series has been as high as 10% (Murphy and Schoenberg, 1967; Schmidt *et al.*, 1973); our results (an incidence of 4%) compare favourably.

In conclusion, our long-term results show a relatively low incidence of late complications but deterioration of the upper tracts has been the main problem. In certain non-malignant cases (*e.g.* neurogenic bladder), because of the doubtful long-term effects on renal function, urinary diversion should be avoided if at all possible. However, if diversion is essential, then in our experience an ileal conduit is still a very acceptable method in adults.

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The Identification of Patients at Risk from Acute Retention

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Summary—Clinical and urodynamic features of patients at risk from acute retention were investigated in 2 retrospective studies. It is suggested that detrusor decompensation may be a cause of acute retention in some individuals. This factor was investigated in a series of patients with outflow obstruction by a method of repeat cystometry.

Acute urinary retention is a common mode of presentation in a patient with bladder outflow tract obstruction. Patients who undergo prostatectomy after an episode of retention have been shown to have a higher incidence of post-operative mortality and morbidity than those undergoing elective surgery (Singh *et al.*, 1973). Blandy (1976) has also maintained that patients with symptoms of prostatism should undergo early surgery to reduce the risk of subsequently developing acute retention.

The purpose of this study was to identify from amongst a series of patients with symptoms of prostatism those at risk from acute retention.

Method

This investigation consisted of 3 separate clinical studies—2 retrospective and one prospective.

In the initial study, 60 male patients over the age of 55 years admitted to the Department of Urology at Southmead Hospital were assessed on admission to hospital with regard to length of history and symptomatology. Group 1 consisted of 30 patients admitted as an emergency with acute urinary retention due to benign prostatic hyperplasia. Group 2 also comprised 30 patients admitted from the waiting list with symptoms of prostatism for routine prostatectomy.

The second study investigated the urodynamic features of patients developing acute retention. All male patients over the age of 55 attending for urodynamic investigation of a variety of lower urinary tract symptoms were followed up over a 3-year period to see which of them subsequently developed acute retention. Twenty-five patients were identified and an analysis of their urodynamic features undertaken.

The results of these 2 previous studies suggested that detrusor failure may be important in the aetiology of acute retention. This factor was investigated in a third study which assessed detrusor failure as a result of bladder overdistension in a series of male patients over the age of 55 years. Thirty such patients were investigated by a technique of repeat cystometry. Six of them were referred with symptoms of outflow obstruction, but urodynamic testing showed them to be unobstructed. The remaining patients were all considered to have outflow obstruction by our criteria (urethral resistance >1.0 cm H_2O/ml^2s^{-2}). Patients with obstruction were then subdivided into 3 groups depending on the presence or absence of motor or sensory urgency. Sensory urgency was defined as an increased periurethral desire that provoked frequency. Those patients with motor urgency needed actively to "hold" their urine, the majority experiencing episodes of urge incontinence (Table 1).

Following an initial free flow rate an 8 FG filling catheter and a 16 gauge epidural pressure line were passed *per urethram*. A measurement of the residual urine was obtained and the bladder was then filled at 60 ml per min with normal

Table 1 Repeat Cystometry (30 Male Patients >55 Years of Age)

	No. of patients
Group I—Unobstructed (control)	6
Group II—Obstructed. No urgency	6
Group III—Obstructed. Sensory urgency	8
Group IV—Obstructed. Motor urgency	10

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Symptomatology (60 Patients)

	Group 1 *Acute retention*	*Group 2* *Prostatism*
Age (years)	69.5 (SE 1.87)	67.0 (SE 1.37)
Length of history (months)	24.9 (SE 6.61)	47.8 (SE 6.74)
Frequency	9.0 (SE 0.80)	9.5 (SE 0.78)
Nocturia	2.1 (SE 0.34)	2.4 (SE 0.31)

saline at 37°C. Three separate cystograms were performed on each patient.

The first cystogram (1) was terminated when the patient experienced his first desire to void, and at the second cystogram (2) filling was stopped at the patient's normal functional capacity. At the third cystogram (3) bladder filling was stopped only when the patient experienced severe bladder pain or persistent leakage from the bladder. After each cystogram the 8 FG filling catheter was removed and the patient voided in the sitting position in private. The order of performing the cystograms was randomly varied at 20-min intervals.

The basic urodynamic measurements of rectal pressure, total bladder pressure and intrinsic bladder pressure (derived by electronic subtraction) and urine flow rate were recorded. Elcomatic pressure transducers (EM 750) and uroflow transducers (EMT 435) were used for these recordings.

Results

Study I

As shown in Table 2, there was no difference between the 2 groups in terms of the patients' age, degree of frequency or nocturia. However, patients with prostatism had a significantly longer past history of urological symptoms compared with those presenting with acute retention (<0.05). Urgency and urge incontinence were more commonly seen in the patients with prostatism (Table 3). Hesitancy of micturition, however, was more commonly found in the group with retention; in particular, 20% of these patients experienced marked hesitancy with a full bladder. Only 76% of those with acute retention had noted previous deterioration in their urinary stream.

Table 3 Symptomatology (60 Patients)

	Group 1 *Acute retention (%)*	*Group 2* *Prostatism (%)*
Urgency	33	80
Urge incontinence	13	40
Hesitancy	60	26
Decreased stream	76	100

Study II

An analysis of the 25 patients presenting with acute retention within 2 years of urodynamic studies showed that only 18 had evidence of classical outflow obstruction with high detrusor pressures and low flow rates. Of the remaining 7 patients, 3 had shown underactive bladders on voiding (detrusor pressure <40 cm H_2O). The remaining patients were regarded as normal on urodynamic investigation apart from a late first desire to micturate (>250 ml) and an increased cystometric bladder capacity (>650 ml).

The voiding studies of the 18 patients with outflow obstruction subsequently presenting with retention were not found to be significantly different from any other group of patients with outflow obstruction. However, the residual urine values in this group were raised.

Study III

The results from Study III showed that bladder capacity increased progressively with the cystograms from 1 to 3 in the 4 groups of patients (Fig. 1). However, the maximum bladder capacity was lower in the groups which were obstructed with urgency of micturition. An increasing bladder capacity in those patients with obstruction resulted in a fall in the maximum detrusor pressure on voiding and this was accompanied by a similar fall in the urine flow rates (Fig. 2). In the unobstructed group a rise in bladder capacity was accompanied by an increase in the volume of urine voided with no significant increases in the volume of residual urine (Fig. 3). However, in the obstructed groups increasing bladder capacity resulted in increasing residual urine volume and,

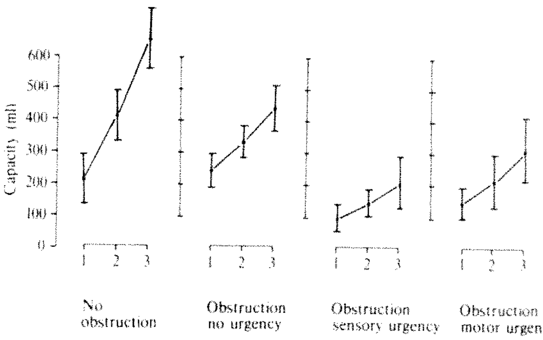

Fig. 1 Bladder capacity. Repeat cystometry.

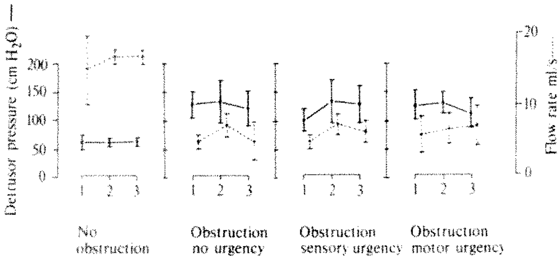

Fig. 2 Detrusor pressure—maximum flow rate. Repeat cystometry.

in the obstructed and obstructed sensory groups, a fall in the volume of urine voided.

Discussion

It is difficult on symptoms alone to identify patients at risk from urinary retention, although hesitancy of micturition, particularly with a full bladder, is a common predisposing symptom. This factor has previously been recognised by Turner-Warwick (1979) as common prior to an episode of retention. There was some evidence to suggest that patients presenting with retention had in fact fewer urological symptoms than those presenting routinely to the urological clinic.

The second study has shown that a proportion of patients presenting with acute retention may not have the so-called classical outflow features of obstruction as defined by urodynamic investigation. In addition, it would appear impossible, on pressure flow studies alone, to predict those patients at risk from retention: the only significant predisposing factor appeared to be a large volume of residual urine. These studies suggested that detrusor function may be a relatively more important factor in patients developing acute retention and that the role of detrusor failure in the genesis of acute retention required further investigation. One of the commonest causes of detrusor failure practice is over-distension of the bladder as a result of the patient postponing the desire to void over a variable period of time.

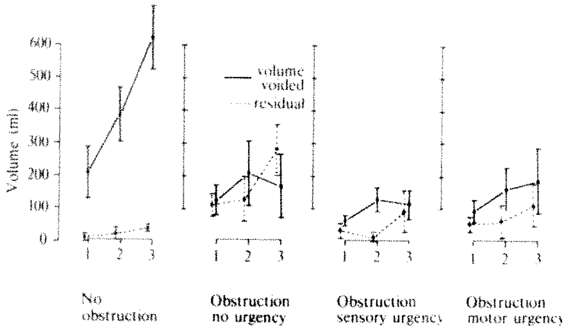

Fig. 3 Volume voided—residual urine. Repeat cystometry.

This theory was investigated in the third study. The results demonstrated that the unobstructed bladder responded to increasing bladder capacity with a rise in the volume of urine voided and that this was achieved without a rise in the detrusor pressure. In cases of outflow obstruction an increasing bladder capacity resulted in varying degrees of detrusor failure, with increasing urinary residual volumes. Bladder decompensation was most marked in that group of patients who were obstructed but did not complain of urgency of micturition. It is suggested that in these patients a rapid rise in bladder capacity associated with a diuresis could precipitate an episode of acute urinary retention.

It is concluded that it is difficult to identify with certainty those patients at risk from acute retention but patients with severe hesitancy and a large volume of residual urine should receive priority on the operating list. Patients with irritative symptoms of prostatism and low residual urines appear to be protected from retention because of their reduced bladder capacity. A frequent cause of acute retention may be bladder failure, not only in patients with evidence of detrusor under-activity but also in those with outflow obstruction as a result of detrusor overdistention.

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Comparison Between Continuous Flow and Intermittent Flow Transurethral Resection in 40 Patients Presenting with Acute Retention

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Summary—Forty patients admitted with acute retention of urine were treated by transurethral resection of the prostate by either the continuous or intermittent flow resectoscope. No significant differences or trends were demonstrated between the 2 techniques in respect of speed of resection, blood loss and amount of glycine absorbed. There was a marked degree of haemodilution during surgery in some patients.

Transurethral resection of the prostate is usually an uneventful procedure in experienced hands. This is due to the quality of modern instruments, the use of non-haemolytic irrigation fluids and improved urological training in endoscopic techniques.

Nevertheless, transurethral resection inevitably leads to some absorption of irrigation fluid and the "TUR-syndrome" is still occasionally seen, usually after a lengthy procedure for a large gland (Elliot *et al.*, 1963). The benefits that have been attributed to continuous flow resection are that it reduces the chance of the TUR-syndrome occurring and extends the potential operating time without the risk of absorption of a large quantity of irrigating fluid (Iglesias and Stamms, 1975). A clinical impression that the continuous flow technique is quicker than conventional techniques has not been substantiated and the suprapubic drainage technique may be more effective in reducing operating time (Holmquist *et al.*, 1979).

Patients and Methods

Forty patients between 52 and 89 years of age presenting with acute retention of urine were randomised into 2 groups. In 20 patients transurethral resection was performed using an Iglesias continuous irrigation 28 FG resectoscope and in the other 20 patients a conventional 26 FG resectoscope was employed; 1.5% W/V glycine solution was used for irrigation. Otherwise the anaesthetic and operative techniques were standardised and one surgeon performed all of the operations. One litre of Ringer-lactate solution was infused intravenously during the procedure and 40 mg of frusemide were given intravenously at the end of resection.

The following observations were made: weight of prostate resected; time of prostatic resection; time to obtain haemostasis; blood loss during surgery; haemodilution during surgery; serial glycine and serine levels every 15 min during surgery and for the first 2 h of the recovery period.

Blood loss was measured by a modification of the oxyhaemoglobin method of Dacie and Lewis (1975) after a pilot study to ensure that glycine did not affect the accuracy of the method. The amount of irrigation fluid absorbed during sur-

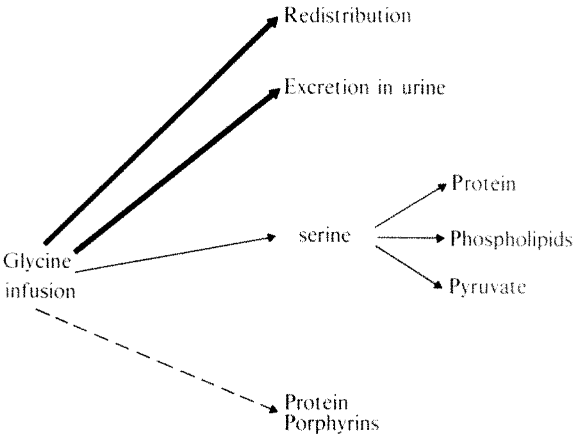

Fig. 1 Pathways followed by glycine after intravenous infusion.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1

Parameter	*Continuous flow*	*Intermittent flow*
Weight of prostate	5-50 g Mean: 21.0 g	5-70 g Mean: 28.5 g
Time of resection	19.4 ± 12.6 min	26.2 ± 14.9 min
Resection/min (g)	1.08 g	1.09 g
Time of haemostasis	6.4 ± 5.5 min	7.8 ± 3.7 min
Total operating time	26.1 ± 16.8 min	34.1 ± 16.9 min
Resection/min total operating time (g)	0.80 g	0.84 g

gery was calculated from the peak serum glycine levels and comparing these with serum glycine levels following the intravenous infusion of a known amount of glycine in sheep. Glycine is the major amino acid in the urine and is rapidly excreted. There is also a rapid redistribution of glycine within the body compartments and although the glycine/serine interconversion normally operates mainly in the direction of glycine formation, this is reversed in the presence of a glycine load and a significant amount of glycine is converted to serine during the period of surgery and recovery (Nyhan and Childs, 1964). As a result, the quantity of glycine in circulation at any one time, which could be simply calculated from the serum glycine levels, represented only about 40% of the volume of glycine infused (Fig. 1).

Results

There was no significant difference or trend between the 2 techniques in the speed of resection or time of haemostasis (Table 1). The mean size of glands resected by the intermittent flow technique was larger and this was reflected in the increased mean period of resection time. There was very little difference between speed of resection of the smaller and larger glands in either group, though the larger the gland the quicker the resection measured in g/min. Interestingly, there was a slight increase in speed of resection in both groups as the series progressed.

Table 2

Parameter	*Continuous flow*	*Intermittent flow*
Blood loss (ml/min)	16.2 ± 12.7 ml/min	17.4 ± 10.4 ml/min
Haemodilution (drop in g/Hb)	2.7 ± 1.7 g	3.1 ± 1.7 g

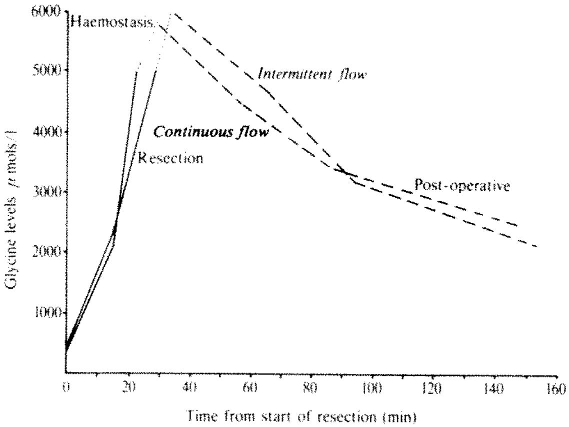

Fig. 2 Serum glycine levels against time in minutes during and after continuous and intermittent flow resection.

There was no difference in the blood loss between the 2 techniques (Table 2), although the estimated amounts seem surprisingly high compared with other series (Madsen and Strauch, 1966).

Although the mean reduction in haemoglobin during surgery, representing haemodilution, is unremarkable, there were 8 patients in whom the reduction in haemoglobin was over 4.5 g; in 3 of these patients it was over 5 g and in one over 6 g. Equally, there was no difference between the peak glycine levels (Fig. 2) or the volume absorbed between the 2 groups (Table 3) and although the glycine levels were higher in patients with large prostates and longer resection times, there were individual long resections for large glands in which very little glycine was absorbed and small glands with a short period of resection in which absorption was very rapid.

Discussion

When Iglesias developed the continuous flow resectoscope (Iglesias *et al.*, 1975) the theoretical advantages seemed clear. It should reduce the operating time by eliminating the time taken for emptying the bladder and the period of reorientation when the working element is replaced; it should reduce the amount of absorption of irrigation fluid associated with increased bladder pressure towards the end of each filling cycle and, perhaps more importantly, it should make difficult bladder tumours, particularly those on the anterior wall and vault of the bladder, easier to resect as the tumour would not float away out of reach of the resectoscope.

However, we found no difference between the 2 techniques of continuous and intermittent flow

Table 3

Parameter	*Continuous flow*	*Intermittent flow*
Peak glycine levels	Range: 2272-10,713 Mean: 5506±3378 μmol/l	Range: 1682-16,408 Mean: 6765±3458 μmol/l
Volume of glycine absorbed	Range: 111-763 ml Mean: 374±213 ml	Range: 87-983 ml Mean: 380±211 ml

by any of the parameters measured, although (purely subjectively) the continuous flow technique did sometimes seem to be easier. There were few technical problems associated with its use, though with the larger glands it was usually necessary to have a break during resection because of the fatigue associated with continual resection.

The amount of irrigation fluid absorbed varied widely but in no instance was it as much as a litre and the only surprising factor was the marked haemodilution that occurred in 40% of the patients. This was not restricted to either group (5 continuous flow and 3 intermittent flow) though it certainly, in part, reflected higher glycine levels, but may also have been related to the well documented inappropriate diuretic response which up to 25% of patients demonstrate with an overload of fluid when undergoing transurethral resection (Holtgrewe and Valk, 1961); it is possible that the greater the fluid load the more likely this abnormal response is to occur.

It is interesting that preference for and against the continuous flow resectoscope for prostatic resection varies greatly between individual urologists, but it is clear that this is a subjective phenomenon. If more rapid resection is considered desirable, then some form of suprapubic drainage technique is more effective, but it seems doubtful whether this is of value except for the very large glands.

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Fluid Absorption During Transurethral Prostatectomy

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Summary—A study of 39 patients having a transurethral resection (TUR) of prostate for benign prostatic hyperplasia was carried out. Large quantities of mannitol, which was used as the irrigating fluid during the procedure, were found to enter the circulation. A corresponding fall in the serum sodium levels was noted. Those patients with serum mannitol levels greater than 4000 mg/l were noted to be hypotensive and have a bradycardia. These patients were nearly all hypovolaemic and the bradycardia was felt to be inappropriate. The possibility of this being due to a combination of factors including intravascular mannitol is considered.

The TUR syndrome is a well recognised complication of transurethral resection of the prostate. It is characterised by hypertension, bradycardia, confusion, hyponatraemia and a reduced serum osmolality (Taylor *et al.*, 1958). Acute blood loss following TUR will lead to tachycardia followed by hypotension if the blood loss is not corrected. Occasionally, in the older patient, hypotension may be seen at the onset of the hypovolaemia. The occurrence, in a number of patients, of hypotension associated with bradycardia seemed to be inappropriate. A study of this phenomenon is reported.

Patients and Methods

Patients undergoing TUR for benign prostatic hyperplasia were studied. The age of the patient and which surgeon performed the operation were noted. A standard anaesthetic technique using nitrous oxide and halothane was employed. The bag containing the irrigating fluid (3% mannitol) was suspended one metre above the symphysis pubis of the patient. At the end of each procedure 40 mg of frusemide were given intravenously. The wet weight of prostatic tissue resected was measured. Blood pressure recordings were taken by the standard method using a sphygmomanometer cuff. Pre-operative and 48 h post-operative haemoglobin levels were measured.

Table 1 Number of Patients Within Each Group According to Weight of Prostate

Group	*Weight of prostate*	*Number of patients*
1	1-10 g	14
2	11-20 g	9
3	21-30 g	9
4	31 + g	7

Blood for the serum sodium and mannitol levels was taken pre-operatively, immediately the operation was completed and 3 h and 24 h post-operatively. The sodium level was estimated using a standard analytical technique. The mannitol levels were measured using aliquots of serum (200 μl) which were deproteinised by the method of Somogyi (Somogyi, 1945). The deproteinised supernatant was then freeze dried with 50 μg of methyl-α-D-mannopyranoside. These dried sam-

Table 2 Weight, Fall in Sodium Level, Mannitol Level and Fall in Osmolality in Each Group*

Group	*Weight (g)*	*Average fall in sodium (mmol/l)*	*Average mannitol level (mg/l)*	*Average fall in osmolality*
1	5 (2-10)	5 (14-+4)	771 (18-2777)	1 (−8-+36)
2	16 (12-20)	4 (0-16)	1211 (135-2917)	5 (−23-+4)
3	26 (22-29)	10 (4-17)	2469 (592-7330)	6 (1-11)
4	46 (31-70)	15 (5-25)	3234 (197-6500)	8 (−19-+5)

*Range in parentheses.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 3 Post-operative Fall in Mannitol Levels

Group	*Average post-op. serum mannitol (mg/l)*	*Average 24-h serum mannitol (mg/l)*
1	771	114
2	1211	89
3	2469	345
4	3234	291

ples were then trimethylsilylated and chromatographed by gas liquid chromatography (Palmano *et al.*, 1977). The sugars were identified by comparison of retention times with those of known standards. The serum osmolality was measured using the depression of freezing point.

Results

There were 39 patients in the study. They were divided into 4 groups according to the weight of prostate resected (Table 1). This was correlated with the serum sodium and mannitol levels in the immediate post-operative specimen (Table 2). There was a progressive fall in the serum sodium levels and an increase in the serum mannitol levels with the size of prostate resected. The mannitol levels rapidly returned to normal (Table 3). The 5 patients with low mannitol levels (less than 150 mg/l) had a steady pulse and blood pressure. The patients with high mannitol levels (Table 4) all, with one exception, had a fall in blood pressure and pulse. Four of these 6 patients required transfusion with blood.

Discussion

The results show that during the performance of a TUR a considerable volume of irrigating fluid may enter the circulation. A serum mannitol level of 4000 mg/l means that over 4 litres of irrigating fluid have entered the circulation (Taylor *et al.*, 1958). The actual quantity of fluid absorbed is not related directly to the weight of prostate resected, but in general those patients having the greater weight resected have higher serum mannitol levels. A corresponding fall in the serum sodium level was noted in these patients. Since the irrigating fluid contains no electrolytes, this fall is inevitable. The fluid is iso-osmolar with serum and therefore no appreciable fall was seen in the serum osmolality.

The patients, who in the early post-operative period had a bradycardia with hypotension, were mostly cases with high serum mannitol, low serum sodium levels and an appreciable blood loss. These patients also had signs of hypovolaemia including pallor, poor peripheral perfusion and a weak pulse. Another group of patients who were not clinically hypovolaemic also had hypotension and a bradycardia. Even if the rate of infusion of intravenous fluid was not increased their blood pressure gradually rose.

Mannitol in the intravascular compartment causes considerable physiological disturbance as it acts not only as an osmotic diuretic but also causes water to move from the intracellular to the intravascular space. Patients undergoing a TUR will therefore be subjected to loss of colloid in the form of blood, a diuresis induced by mannitol and frusemide and contraction of their intercellular compartment. It is possible that a combination of all of these factors leads to the occurrence of hypotension with the inappropriate bradycardia. As this can occur in both hypovolaemic and normovolaemic patients, particular attention should be paid to the clinical state before deciding that blood infusion or another colloid is needed.

It is concluded that during TUR of the prostate up to 7 litres of irrigating fluid may enter the circulation. This study suggests that, if this fluid is 3% mannitol, some of the signs of hypovolaemia may

Table 4 Results in Patients With High Mannitol Levels

Mannitol (mg/l)	*Sodium fall (mmol/l)*	*Osmolality fall*	*Prostate weight (g)*	*Hb. fall (g/dl)*	*Blood pressure*	*Pulse (per min)*	*Blood required*
4406	12	4	12	5.2	↓	75	No
3725	17	6	22	2.0	↓	80	Yes
6500	25	7	53	1.6	↓	90	No
4229	14	14	60	1.6	↓	80	Yes
5091	17	1	70	0.3	↓	60	Yes
4116	21	2	33	0.7	↓	60	Yes

be masked. The clinical assessment to distinguish between those who are hypovolaemic and those who are not is therefore extremely important.

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The Unstable Bladder and Prostatectomy

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Summary—Cystometry was carried out on 51 male patients presenting with frequency, urgency and a poor urinary stream. Twenty-four obstructed and unstable patients were referred for prostatectomy and underwent repeat cystometry at intervals after the operation.

Forty-one per cent of patients became stable by 6 months and no patient reverted to stability after this time. Grading of pre-operative instability according to the provoking stimulus was of value in forecasting improvement. A voiding pressure of over 100 cm of water before operation was associated with a good result.

Precipitancy of micturition in the middle-aged and elderly man is a common problem in urological clinics and it can be a difficult decision whether or not to advise prostatectomy. Urodynamic investigation usually demonstrates that these patients have an unstable bladder and there may also be evidence of bladder outflow obstruction. It is widely believed that in a proportion of patients who show bladder instability and outflow obstruction the cystometrogram will convert and become "stable" after relief of the obstruction. However, this belief is not adequately supported in the literature and it is not known when this conversion occurs and if it correlates with subjective improvement. In an attempt to answer these questions we have selected a group of patients who were demonstrated to be both unstable and obstructed at their initial assessment and have had repeated cystometry at intervals after prostatectomy.

Patients and Methods

Male patients with symptoms of urgency, frequency and poor urinary stream were referred for investigation. Those over the age of 70 and those with overt neurological disease were excluded.

Filling and voiding cystometry was carried out on all patients and those who were shown to be both unstable and obstructed were referred for prostatectomy.

Instability was defined as the occurrence of bladder contractions of more than 15 cm of water which the patient was unable to inhibit. Instability was graded according to the provoking stimulus, 6 grades being recognised; these were: A. Instability on supine filling, B. on coughing, C. on standing up, D. on coughing while standing, E. on heel jumping, F. on heel jumping and coughing.

The diagnosis of obstruction was usually obvious with a high voiding pressure and low flow rate and all patients had a urethral resistance factor (P/F^2) of more than 0.4. Prostatectomy was followed by repeat urodynamic tests at intervals. Most patients agreed to undergo repeat investigations and over 100 examinations were carried out without any complications apart from one episode of symptomatic urinary infection.

Results

A total of 51 patients have been studied (Table 1). Twenty-nine were both obstructed and unstable and were referred for prostatectomy and formed the basis of this study. Two are still awaiting operation and 3 refused further tests, so that results in 24 patients are presented. Twenty-two patients out of the original 51 were eliminated after initial assessment: 10 were obstructed but stable, 8 were not obstructed but unstable and 4 were normal.

Table 1 Urodynamic Diagnosis in 51 Male Patients With Frequency, Urgency and Poor Stream

Obstructed and unstable	29 (57%)
Obstructed and stable	10 (19%)
Not obstructed but unstable	8 (16%)
Normal	4 (8%)

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Results 3 Months After Prostatectomy in 24 Patients

	Symptom free	*Urgency or urge incontinence*
Stable	4	3
Unstable	4	13
Total	8	16

Three Months

Of 24 patients, 8 were symptom-free, 8 complained of urgency only and 8 complained of urge incontinence. Seven of the patients were stable (29%) and only one was still obstructed. Four of the 8 symptom-free patients were stable compared with 3 of the 16 patients with urgency and/or urge incontinence (Table 2).

Six Months

Eighteen patients were followed up for 6 months and 8 were stable. Thirteen (72%) felt an improvement and 11 of the 13 were stable or proved to have a change in the grade of their instability. Five (28%) had not been improved and 4 of the 5 had no change in the grade of instability, while one was still obstructed. Ten patients have been followed for 9 months, 6 for a year and 4 for 18 months and no patient has converted to stability after 6 months.

Certain parameters in the initial assessment were examined critically for prognostic factors. The pre-operative grade of instability was different in patients who became stable from those who did not. Only 2 of the 11 patients who were unstable on supine filling (grades A, B) became stable after operation, while 6 of the 7 patients who were shown to be unstable only after standing up (grades C, D, E, F) became stable after operation.

The pre-operative voiding pressures were significantly different in the stable and unstable groups (Table 3). The reduction in voiding pressure after operation in the 2 groups was also significantly different. The mean bladder capacity before operation in the subsequently stable group was 468 ml and in the unstable group was 254 ml, the difference being highly significant. However, several parameters were not significantly different between the subsequently stable and unstable groups. They included age, pre-operative flow rate, urethral resistance factor, compliance and the magnitude of the unstable contractions. Post-operative calculations of change in flow rate, resistance factor, capacity and compliance were also not significantly different.

Discussion

Only 57% of patients who complained of urgency, frequency and poor urinary stream were both obstructed and unstable on objective assessment. Six months after operation 41% (7 out of 17) of the obstructed unstable patients whose obstructions had been relieved were stable. One patient, although stable, was still obstructed.

Andersen (1976) and Abrams (1977) have reported similar studies of patients who converted and became stable 6 months after prostatectomy, but in their studies the patients were not selected and were on a waiting list for prostatectomy. In the series reported by Rao and his colleagues (1979) 82% became stable but they employed only supine cystometry.

In our study 72% of patients were symptomatically improved and this improvement was associated with stability or with a change in the grade of instability in the majority of cases. We decided on the grades of instability for convenience at cystometry but where the grade changed it was always in the direction from A to F or from instability provoked by supine filling to instability provoked by change of posture. Patients were asked to stop taking anticholinergic drugs before the

Table 3 Urodynamic Data in the Subsequently Stable and Unstable Groups

	Stable patients (8)	*Unstable patients (10)*		
Mean pre-operative voiding pressure (cmH_2O)	115 ± 56	70 ± 19.5	t = 2.301	$P<0.05$
Mean reduction in voiding pressure after operation	55%	26%	t = 2.231	$P<0.05$
Mean pre-operative bladder capacity (ml)	468 ± 160	254 ± 138	t = 3.057	$P<0.01$

cystometry but 2 at their 9-monthly visit were taking propantheline and their instability grades had changed from A to E. On stopping the tablets the grade returned to A at the next assessment.

It was useful to grade instability according to the provoking stimulus. Patients who were unstable on supine filling (grade A) before operation were less likely to become stable after operation and also were less likely to be symptom-free.

The mean pre-operative voiding pressure was significantly different in the subsequently stable and unstable groups, as also was the mean percentage reduction in voiding pressure in the 2 groups. So it seems that in patients with urgency and some objective evidence of instability and obstruction, those with the clearest evidence of obstruction do well after prostatectomy.

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The Treatment of Patients with Urinary Incontinence after Prostatectomy

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Summary—Seventy-seven patients were treated for incontinence after prostatectomy for benign prostatic hypertrophy. Forty-six patients had detrusor instability and 28 had stable bladders. No cause for the incontinence was found in 3 patients. The majority of the group had sphincter damage (74%).

Conservative treatment other than drugs was all that was required in 22 patients, but drugs such as Eskornade, imipramine or emepronium were used in a further 19. Some symptomatic improvement occurred in 53% of these 19 patients. Surgery was required in 38 cases (relief of obstruction endoscopically in 11, insertion of prosthetic devices in 27). Endoscopic treatment rarely effected a cure, but the results with prostheses were satisfactory, a cure or improvement occurring in 65% of the patients, with a low complication rate.

The occurrence of incontinence after prostatectomy is usually a surprise to the surgeon and always a burden for patient and surgeon alike. In most cases, perhaps with supportive therapy, time effects a cure, but in the remainder further treatment is required.

The management of these patients has for a long time consisted of physiotherapy and re-education of the external sphincter, but drugs and further surgery have contributed considerably to the patients' well-being. In particular, the introduction of prostheses has improved the outlook for patients with persistent incontinence (Kaufman, 1970, 1973).

The investigation of patients complaining of post-prostatectomy incontinence has been described previously, along with the necessity to recognise the presence of detrusor instability in addition to sphincter damage as factors contributing to the patients' symptoms (Fitzpatrick *et al.*, 1979). We report here on the results of treatment of this distressing condition.

Patients and Methods

Seventy-seven patients were referred to the Urodynamic Department, Institute of Urology, over a 45-month period for investigation and treatment of persistent incontinence after prostatectomy. Instability was defined as an end-filling pressure greater than 20 cm H_2O with or without unstable detrusor contractions during filling. Sphincter damage was indicated by inability to arrest micturition and maintain that state during videocystography.

Conservative treatment (apart from drugs) was all that was required in some patients. Advice was offered on the best methods for controlling incontinence such as physiotherapy, faradism and the anal plug continator or, infrequently, the penile clamp. If drugs were required it was often necessary to assess the response to a variety of agents either singly or in combination until the best regime for each individual was apparent. The drugs used were emepronium, Eskornade (a proprietary preparation of isopropamide, phenylpropanolamine and diphenylpyraline), imipramine and a combination of the 2 latter drugs. Surgical treatment involved the insertion of prostheses as described by Kaufman and Raz (1979), Rosen (1976) and Scott *et al.* (1974), or the endoscopic relief of residual obstruction.

The patients were followed up for a mean period of 20 months, with a range of 4 to 40 months.

Results

In our previous communication (Fitzpatrick *et al.*, 1979) it was found that most patients had

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Urodynamic Findings

Stable		28 (36%)
Unstable		46 (60%)
Sphincter damage	29	
Residual obstruction	8	
Both	2	
Normal		3 (4%)
Total		77 (100%)

sphincter damage with or without detrusor instability, the latter being a common finding, and this is still the case in this series (Table 1). In all, 74% of these patients had damage to their distal sphincter mechanism.

The patients can be divided into 3 groups on the basis of treatment:

Group 1 Conservative management apart from drugs (22 patients).
Group 2 Drug treatment (19 patients).
Group 3 Surgical treatment (38 patients)—prostheses in 27; further endoscopic treatment in 11.

The proportion of patients with or without detrusor instability was the same in each treatment group (Table 2). One patient who initially had a prosthesis inserted with an unsuccessful result and a second patient who had a further transurethral resection (TUR) were later treated with drugs and are included in both Group 2 and Group 3, explaining the apparent numerical disparity. Two patients underwent definitive treatment at the time of endoscopy and did not require further investigation. In another 2 patients replacement prostheses were required after removal of the first prosthesis.

Group 1

Five patients in this group could have benefited from further surgical treatment but did not receive it because one patient refused and 4 were considered medically unfit. In the remainder, the conservative measures described above kept the patient dry enough for no further treatment to be required.

Table 2 Treatment of Post-Prostatectomy Incontinence

	N	*Conservative treatment*	*Drug treatment*	*Operative treatment*
Stable	28	8 (29%)	6 (21%)	14 (50%)
Unstable	46	11 (24%)	13 (28%)	22 (48%)
Normal	3	3 (100%)	—	—
Total	77	22	19	36

Table 3 Drugs Used

	N	*Cured*	*Improved*	*Failure*
Eskornade	12	1	6	5
Imipramine	3	1	0	2
Eskornade + Imipramine	2	1	1	0
Emepronium	2	0	0	2
Total	19	3 (16%)	7 (37%)	9 (47%)

Group 2

Drug treatment was useful in 53% of the patients in whom it was the definitive treatment (Table 3), but only 16% pronounced themselves cured. Eskornade was the most satisfactory drug and was also the most commonly prescribed. Side effects (such as dry mouth) occurred and sometimes necessitated withdrawal of the drug.

Group 3

This group included patients treated endoscopically for relief of residual obstruction (TUR, bladder neck (BN) incision, external sphincterotomy) as well as patients in whom prostheses were inserted. Patients who had endoscopic treatment are shown in Table 4. Only one in this group was cured, and he simply had endoscopic removal of nylon which had been used to close the prostatic capsule and was lying in the urethra. None of the patients who had definitive treatment was cured, although half of them had some symptomatic improvement.

Twenty-nine prostheses were inserted into 27 patients, all of whom had sphincter damage and 14 of whom had evidence of detrusor instability. Twenty-two Kaufman prostheses were inserted,

Table 4 Group 3 Results of Endoscopic Surgery

	N	*Cured*	*Improved*	*Failure*
TUR	6	0	2	4
BN incision	2	0	2	0
External Sphincterotomy	2	0	1	1
Removal of nylon	1	1	0	0
Total	11	1	5	5

Table 5 Group 3 Results of Prostheses

	N	*Cured*	*Improved*	*Failure*
Kaufman	22	11	4	7
Rosen	6	2	1	3
Brantley Scott	1	1	0	0
Total	29	14 (48%)	5 (17%)	10 (35%)

as well as 6 Rosens and one Brantley Scott device. It is interesting to note that in the majority of cases (65%) the prosthesis either cured the patient or effected a significant symptomatic improvement (Table 5).

Local complications producing failure included a perineal fistula or urethral erosion in 3 patients, infection and local abscess formation in 2, and delayed rupture of one Kaufman device. One further patient has a chronic perineal sinus but clinical improvement has been maintained. Only one patient developed significant post-operative morbidity (deep venous thrombosis and pulmonary embolus), but there were no deaths.

Discussion

It was mentioned previously (Fitzpatrick *et al.*, 1979) that the urodynamic investigation of post-prostatectomy incontinence is best delayed for 12 months, since it may take this length of time for the detrusor instability associated with outflow obstruction to disappear. During this period, symptoms are best treated by conservative non-invasive means, and most patients require no treatment whatsoever.

As stated above, the symptom of urinary incontinence after prostatectomy remains in a certain number of patients, but surgical treatment was required in less than half of the patients in this series. Conservative measures such as physiotherapy, faradism or anal plug were often satisfactory, but sometimes drugs were required. Although very few were actually cured of their symptoms by drugs, the majority of those in this group received some improvement. Eskornade was the most successful, but side effects slightly limited its use. In fact, attempts are being made to obtain pure phenylpropanolamine, the active ingredient.

In the earlier patients who had prostheses implanted, a urethral catheter was used and retained for 12 days after surgery, but it was felt that the urethral erosions were due to this and so more recently a urethral catheter has not been used. Only 2 patients have required suprapubic catheterisation for urinary retention in the early post-operative period, but after removal of this catheter, urine could be passed *per urethram* without difficulty.

Some patients required adjustment of their implant by injection after the operative oedema had settled. In this series, 11 patients required a total of 18 injections. The technique is simple, Myodil being injected under X-ray screening into the prosthesis, which can easily be felt under the skin. It may be that attaching the device posteriorly with staples on the pubic arch, rather than relying on looping the tapes around the crural insertions, which are in some cases rather feeble, would result in better fixation and reduce the necessity for subsequent injection (Kaufman and Raz, 1979).

In this series the presence of detrusor instability in patients with sphincter damage did not contraindicate the insertion of a prosthesis. Failure of the prosthesis occurred equally in the stable and unstable patients. It is also interesting to note that the mean end-filling pressures were similar in the unstable patients with successful and unsuccessful results to their operations.

Post-prostatectomy incontinence is an uncommon complication and in most cases is amenable to conservative management. The insertion of a prosthesis for incontinence due to sphincter damage is associated with a cure or improvement in the majority of cases.

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The Diagnosis of Oestrogen Escape and the Role of Secondary Orchiectomy in Prostatic Cancer

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Summary—The criteria for the diagnosis of progression of prostatic cancer after primary treatment by androgen suppression (oestrogen escape) were studied in 30 patients. Objective criteria are essential for this diagnosis and in this study the bone scan was the most useful criterion.

Twenty-one of these patients had a secondary orchiectomy: one patient showed a partial objective response and 3 had a subjective response. It is concluded that an orchiectomy following failed primary oestrogen therapy is an ineffective procedure and therefore unjustifiable and that alternative treatments must continue to be evaluated

Androgen suppression by either oestrogen therapy or orchiectomy has remained the basis of treatment of prostatic cancer since it was advocated by Huggins and Hodges in 1941. However, the pattern of response to this hormonal manipulation shows that the duration of hormonal sensitivity is variable: a small proportion of patients never respond whilst others, a majority, eventually show progression of the tumour and are considered to have become resistant to androgen suppression. The term "oestrogen escape" has been used as a convenient expression to describe this event in the course of the disease. Whether the previously suppressed tumour escapes or whether oestrogen resistant cells eventually dominate is not known. At this stage it is common practice to try other forms of treatment. The use of alternative oestrogens or larger doses of oestrogens is popular and an orchiectomy is also often recommended in the hope of gaining further androgen suppression. Whether or not these measures produce a response is debatable mainly because the exact definition of the term "oestrogen escape" is variable and can only be made with confidence when there are objective criteria to evaluate.

We have studied a group of patients with histologically proven prostatic cancer, all of whom eventually showed oestrogen escape. The duration of primary responsiveness and the mode of escape was recorded and related to the stage of the disease and histological grade at presentation. The sensitivity of the criteria and especially the objective measurements used in diagnosing oestrogen escape have been assessed. The response to a secondary orchiectomy was then examined in detail according to these criteria.

Table 1 Investigation Protocol at Presentation

1. Serum acid phosphatase estimations (at least 2 estimations)
2. Serum alkaline phosphatase estimation.
3. Excretion urogram.
4. Chest X-ray.
5. Isotope bone Scan, followed by X-ray of abnormal scan areas.
6. Bimanual examination under general anaesthetic.
7. Biopsy (Tru-cut or transurethral resection).

Patients and Methods

Thirty patients with histologically proven prostatic cancer were studied. At presentation, all patients were investigated according to a protocol (Table 1) and classified according to UICC (1978) recommendations. Only T and M categories were assessed in this study.

All patients were then treated with some form of hormonal therapy (Table 2) and then followed

Table 2 Hormone Therapy at Presentation

1. Stilboestrol 1 mg tid	14
2. Dienoestrol 5 mg	9
3. Cyproterone acetate 100 mg bd	4
4. Subcapsular orchiectomy	3

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Table 3 Follow-up Investigation Schedule

3 Months—1. Rectal examination
2. Acid phosphatase estimation
3. Alkaline phosphatase estimation

6 Months—1, 2, 3 and
4. Chest X-ray
5. Bone scan plus X-ray of abnormal scan areas.

12 Months—1, 2, 3, 4, 5 and
6. Excretion urogram.

in a special "prostate" clinic (Table 3). Response to treatment was assessed according to the criteria shown in Table 4. These criteria are based on those used by the British Prostate Group (Chisholm, 1980) with inclusion of the bone scan in the objective regression group.

The diagnosis of oestrogen escape in this study was based almost entirely on the criteria shown for objective progression. In one case no objective deterioration was recorded but subjectively the patient deteriorated.

Following the diagnosis of oestrogen escape subcapsular orchiectomy was carried out on all patients who had been treated primarily with either oral oestrogens or cyproterone acetate, the suppressive oestrogen being stopped at this time.

Those patients who had had an orchiectomy as primary treatment were started on a chemotherapeutic regime of cyclophosphamide, razoxane and prednisone at the time of diagnosis of oestrogen escape; this regime was also given when failure to respond to secondary orchiectomy was documented.

Table 4 Assessment Criteria

Objective progression—any one of the following:

1. Increase in primary tumour by one or more T categories.
2. Increase in tumour area by 50%.
3. Maintained increase in serum acid phosphatase levels (at least 2 estimations).
4. New bone lesions or increase of abnormal activity on bone scan.
5. New bone lesions on X-ray.

Objective regression—any one of the following:

1. Decrease in primary tumour by one or more T categories.
2. Decrease in primary tumour area by 50%.
3. Maintained decrease in serum acid phosphatase levels (at least 2 estimations).
4. Decrease in number or activity of lesions on bone scan.
5. Reclassification of osteolytic lesions on X-ray.

Stable disease—all of the following:

1. Stable scan.
2. Stable phosphatase.
3. Stable T category.
4. Stable X-ray appearances.

Table 5 Tumour Classification at Presentation

T Category				
T0	T1	T2	T3	T4
3	0	4	19	4
M Category				
M0	M1			
4	26			

Six patients received radiotherapy to painful bone metastases after the instigation of chemotherapy. One patient commenced a second course of chemotherapy after the failure of the initial course and one patient had a transsphenoidal hypophysectomy after chemotherapeutic failure.

Results

The ages of the patients in this study at presentation ranged from 58 to 82 (average 70). T and M categories and histological grading at presentation are shown in Tables 5 and 6.

Response to Primary Treatment

Five patients (17%) showed no response to primary treatment and continued to progress. Sixteen patients showed objective evidence of regression and the remaining 9 had no change in the objective measurements of the disease. All of the patients showing objective regression improved subjectively, *i.e.* there was a reduction in bone pain and/or improved activity assessment.

Period of Hormonal Responsiveness

In consideration of the 25 patients who showed some response to primary treatment, the minimum time to oestrogen escape was 4 months and the maximum was 8 years (average 29 months).

Mode of Escape

Seventeen patients complained of new or progressive bone pain at the time of diagnosis of oestrogen escape by objective measurements (symptomatic escape). The remaining 13 cases at

Table 6 Histological Grade at Presentation

Differentiation	*No.*
Well	15
Moderate	8
Poor	7

Table 7 Objective Evidence of Escape

Bone scan, first evidence	16
Bone scan only evidence	3
Bone scan and acid phosphatase	6
Bone scan + acid phosphatase + X-ray	1
Acid phosphatase only (equivocal bone scan)	2
Lymphadenopathy + acid phosphatase (normal bone scan)	1
Equivocal objective measures	1

the time of study had no obvious symptomatic change and escape was based on objective evidence alone (asymptomatic escape). The objective evidence for oestrogen escape in this study is shown in Table 7.

In 12 cases the deterioration seen on the bone scan preceded the onset of symptoms.

Subcapsular Orchiectomy

Subcapsular orchiectomy was carried out in 21 patients following the diagnosis of oestrogen escape. Only one patient showed a partial objective response and 3 patients showed a subjective response (Table 8).

Follow-up

At the time of this study 17 patients had died. In these patients, survival after diagnosis of escape ranged from one month to a maximum of one year. The longest survival time in this series was 21 months.

Discussion

The phenomenon of "oestrogen escape" is a common problem in the management of carcinoma of the prostate. A special "prostate" clinic affords an opportunity to observe and document this event and it is also an opportunity to test the value of the criteria used to make the diagnosis of escape.

Table 8 Response to Secondary Orchiectomy in 21 Patients

1. *Objective response*	
Regression	1
Progression	15
Stable	4
Died before evaluation	1
2. *Subjective response (pain, activity assessment)*	
Improved	3
Deteriorated	11
No change	6

Any treatment offered at this stage of the disease is usually palliative for symptoms and its effects temporary. In order to devise effective treatment of oestrogen escape, its diagnosis must be precise and any response to this treatment must be monitored objectively.

In this study we followed the course of oestrogen escape in prostatic cancer with objective criteria, in order to find the most sensitive method of diagnosis and to evaluate the response to further hormonal manipulation such as orchiectomy.

Several theories of oestrogen escape have been postulated. Franks (1976) suggested that all hormonally sensitive tumours will contain a proportion of cells that are not destroyed by this therapy. Following treatment, these cells will be selected out and the onset of escape depends on the proportion of these cells at presentation. Thus the expression "oestrogen escape", while being convenient, may not be an entirely accurate description of the pathological process.

Hanafy *et al.* (1972) found significant testicular atrophy, prominent Sertoli cells and anaplastic prostatic histology in a group of oestrogen refractory patients. He postulated the presence of an oestrogen-dependent prostatic neoplasm and suggested the use of testosterone in these patients.

On considering the presenting features of the patients in this study, the prognostic significance of each factor varied considerably. For instance, the age range was similar to that of our other clinic patients, and there was no preponderance of younger patients in this series. The distribution of T categories showed a significantly larger number of locally advanced tumours (T2-4) in this group (90%), compared with all patients presenting to our clinic with prostatic cancer (75%).

Eighty-six per cent of patients in this series presented with evidence of metastatic disease, whereas only 59% of prostatic cancer patients in our recent experience have evidence of M1 disease at presentation.

Nissen *et al.* (1977) have recorded the prognostic value of clinical staging and histological grading. In our series, 50% of patients presented with well differentiated tumours and only 23% had poorly differentiated tumours. There was no significant difference between these figures and the distribution of histological grading in all of our patients.

The duration of hormonal responsiveness varied considerably and did not correlate with the stage of the disease at presentation or histological grading.

In the diagnosis of escape, the bone scan was consistently more sensitive than the other objective measurements and often preceded the onset of symptoms by several months.

Hormonal manipulation in carcinoma of the prostate continues to be discussed despite its established place in the management of the disease. In 1941 Huggins and Hodges reported the good response of patients to either orchiectomy or oral oestrogens. Nesbit and Baum (1950) concluded that oestrogens plus orchiectomy were better than oestrogens or orchiectomy alone for patients presenting with advanced tumours. The VACURG (1964) studies did not substantiate this, and suggested that more patients died of the cardiovascular complications of oestrogen therapy than from the malignancy. Additional work presented by Jordan *et al.* (1977) suggested that oestrogens were more effective than orchiectomy in preventing cancer death and that the addition of orchiectomy to oestrogens did not offer any clear-cut advantages. In contrast, White *et al.* (1977) reported advantages in the combination of oestrogen and orchiectomy and recorded survival rates in advanced tumours similar to those reported by Nesbit and Baum (1950).

In our practice, patients presenting with evidence of metastatic disease with or without symptoms were treated by some form of androgen suppression (Table 2). The substitution of subcapsular orchiectomy for oestrogen or cyproterone acetate after oestrogen escape did not influence the objective progression of the disease and only occasionally produced a subjective response of any significance. Although this form of secondary hormonal manipulation is common in urological practice (Shuttleworth and Blandy, 1976), few clinical studies supporting its use have been published. Biorn *et al.* (1979) reported a retrospective review of 29 cases of oestrogen escape patients treated by secondary orchiectomy: they reported significant subjective response, and 5 out of 29 patients showed objective evidence of regression. In contrast, we conclude that oestrogen escaped prostatic cancer is unresponsive to any further form of androgen suppression and it is suspected that in those cases where response is reported following orchiectomy, then the criteria for oestrogen escape may not have been as strict as those which we have used.

The poor survival of patients in this series following the diagnosis of escape indicates the aggressive nature of the tumour after this event. Although earlier diagnosis of escape can be affected by regular follow-up, including serial bone scans, it remains to be shown whether alternative treatments, using either chemotherapy or pituitary ablation, alter the natural history of the tumour.

If oestrogen resistant or oestrogen escape patients could be identified earlier by, for example, analysis of tumour tissue for hormone receptors or other tissue markers of hormone responsiveness, alternative potentially curative treatment by radiotherapy or chemotherapy could be used at the time of diagnosis, perhaps preventing the onset of oestrogen escape completely.

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The Role of Urethral Sensation in Clinical Urology

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Summary—The results of testing posterior urethral electrosensitivity in a variety of urological conditions are demonstrated and the relationship between urethral sensitivity and the standard urodynamic investigations discussed. The clinical features of a group of patients with urethral hyposensitivity are presented.

Micturition and urinary continence are now considered to be a function of a series of integrated reflexes. The normal function of these reflexes requires intact motor and sensory components.

Urological investigations have previously concentrated on the motor function of the detrusor and urethra in the analysis of micturition disorders. Bladder and urethral sensation, however, are an equally important, though often neglected, part of these investigations.

Although a variety of sensory receptors have been described in both bladder and urethra, the most potent facilitative receptors for the micturition reflex are situated in the posterior urethra (Mahony *et al.*, 1977). However, standard cystometry fails to give accurate information on the exteroceptive sensory qualities of this region.

Kiesswetter (1977) first applied the technique of mucosal electrosensitivity to both bladder and urethra. He developed a double-barrelled catheter bearing 2 wire electrodes, and by the use of a constant current stimulator was able to quantify a variety of post-operative sensory defects caused by scarring.

The purpose of this study was to assess the importance of urethral sensitivity in a wide range of clinical conditions.

Patients and Methods

Over a period of 12 months the urethral sensitivity of over 100 patients was investigated; all had been referred to the Clinical Investigation Unit at Ham Green Hospital for the investigation of lower urinary tract disorders.

The technique employed in the quantitation of urethral sensitivity was based on the mucosal electrosensitivity method of Kiesswetter (1977). A 10 FG Dover catheter was used in the construction of the electrosensitivity catheter. Two platinum electrodes were mounted 1 cm apart and 1.5 cm below the balloon of the catheter and 2 copper wires connected to these electrodes passed down the lumen of the catheter, the distal end of which had been sealed.

After completion of standard urodynamic investigations consisting of a free flow rate, urethral pressure profile and cystometry, the electrosensitivity catheter was passed into the bladder and the balloon inflated. The catheter was withdrawn until the balloon fitted snugly at the level of the bladder neck; at this point the electrodes were accurately situated in the posterior urethra.

The catheter was connected to a constant current stimulator (Grass CCUI) supplying square wave impulses at a rate of 20 per second. The intensity of the constant current increased slowly from zero until the patient experienced a sensation of burning or tingling. Three separate readings were taken and the mean of these values recorded as the urethral sensitivity threshold.

Thus patients requiring a very low current to produce sensation were described as "hypersensi-

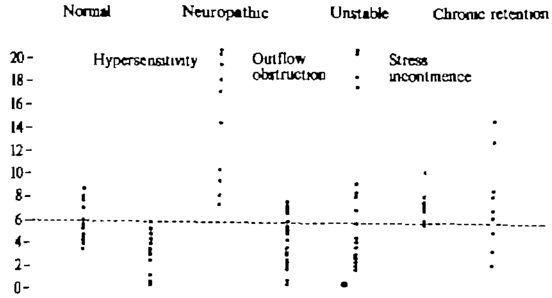

Fig. 1 Urethral electrosensitivity.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

tive" with an increased urethral sensitivity, whereas patients who required a high current to stimulate sensation were said to be "hyposensitive" with a reduced urethral sensitivity.

Results

The urethral electrosensitivity values of the first 84 patients examined by this technique are shown in Figure 1. The patients have been divided into clinical groups which have been substantiated by urodynamic studies. Bladder hypersensitivity refers to patients with symptoms of frequency and urgency who are shown to have a normal cystogram with reduced capacity (Torrens and Abrams, 1979). These patients have been shown to have hypersensitive urethras, and this is also true of the group of patients with outflow obstruction. The group termed "neuropathic" comprises a wide variety of neurological bladders and the results show that the majority of these patients had evidence of urethral hyposensitivity. It is of interest that a number of patients with chronic urinary retention and a smaller number of patients with stress incontinence also had high urethral sensitivity readings. Among the patients with urgency and urge incontinence associated with detrusor instability there was a wide scatter of values over the whole electrosensitivity range, but there were several patients, particularly in the elderly age group, who had very hyposensitive urethras.

In order to assess urethral sensitivity further a comparison was made between the urethral electrosensitivity values and cystometric findings on a standard urodynamic investigation. The patients were divided into 2 groups—those with normal cystograms and those with unstable bladders at cystometry. Patients with evidence of neurological bladder dysfunction were excluded.

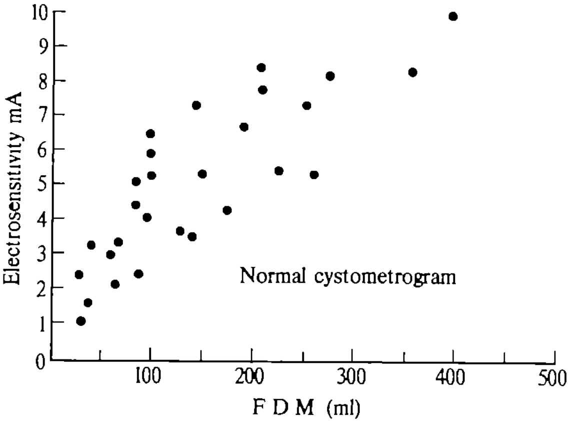

Fig. 2 Urethral electrosensitivity—first desire to micturate (FDM).

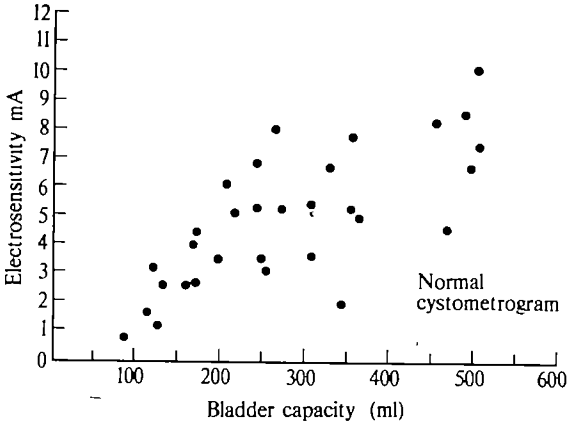

Fig. 3 Urethral electrosensitivity—bladder capacity.

In patients with normal cystograms (Fig. 2) a statistically significant correlation was shown between urethral electrosensitivity and the first desire to micturate (t = 9.20 d.f. 29). A similarly good correlation between urethral electrosensitivity and cystometric bladder capacity is demonstrated in Figure 3 (t = 8.45 d.f. 29). This confirms that bladder capacity is related to urethral sensitivity.

By comparison, those patients with evidence of bladder instability showed no correlation between urethral electrosensitivity and the first desire to micturate (t = 1.74 d.f. 24), or cystometric bladder capacity (t = 0.19 d.f. 24).

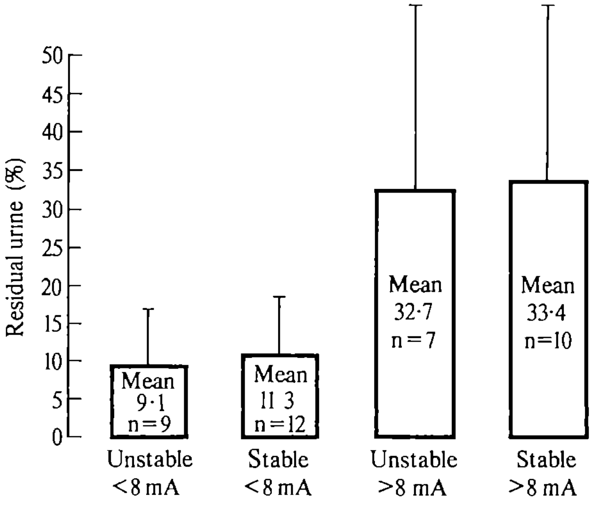

Fig. 4 Urethral sensitivity and balanced bladder function.

In order to investigate urethral hyposensitivity in detail, all patients with sensitivity values greater than 8 mA were compared in a separate analysis. The aim of this study was to assess urethral hyposensitivity in isolation and therefore all patients with evidence of other abnormalities of the detrusor or outflow tract were excluded. Bladder function in these patients was assessed by

$$\frac{\text{Residual urine}}{\text{Bladder capacity}} \times 100$$

as used by Bors (1957) to detect unbalanced neurological bladders. Balanced bladders from this equation should have residual urine volumes of less than 10%. The results of applying this equation to patients with urethral hyposensitivity and comparing them with a group of patients with normal sensitivities are shown in Figure 4. This shows that patients with raised urethral sensitivities have evidence of unbalanced bladders irrespective of whether the bladders are stable or unstable.

Discussion

The investigation had demonstrated the results of testing urethral sensitivity in a variety of urological conditions. A good correlation has been shown between the electrosensitivity measurements and the standard urodynamic findings in patients with normal cystograms. The lack of correlation between these factors in patients with unstable cystograms may indicate an abnormality of the micturition reflex arc which requires further investigation.

Of particular interest are those patients with urethral hyposensitivity. They have been shown to have a high incidence of unbalanced bladders, thus confirming that abnormalities of bladder function may be secondary to deficits of sensation with an intact motor component. Patients with frequency and urgency associated with urge incontinence are recognised as having a high incidence of bladder instability. This investigation has shown that a proportion of these cases have evidence of urethral hyposensitivity. However, a similar group of patients with hyposensitive urethras has also been identified in a number of patients with normal cystometry. These individuals often complain of hesitancy of micturition with a variable stream, recurrent urinary infections and, in a few cases in younger men, recurrent episodes of acute retention.

Urethral sensitivity measurement has been shown to be a reliable, repeatable method of quantifying urethral sensitivity, and has demonstrated the wide variety of syndromes associated with different levels of urethral sensitivity seen in urological practice. Furthermore, this study has identified a group of patients with unbalanced bladders with evidence of isolated urethral sensitivity deficits. Such patients may complain of symptoms similar to those of outflow obstruction.

Acknowledgements

We are grateful to the urologists of the Avon Clinical Area for allowing us to investigate patients under their care, and to the Medical Research Council for financial support (Project Grant No. 974/135). Our thanks also go to Mr Douglas James of the Incontinence Unit, Royal Devon and Exeter Hospital, for his assistance in the construction of the sensitivity catheters.

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Visual Internal Urethrotomy

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Summary—Seventy-one patients with urethral strictures were treated by internal urethrotomy with the Storz-Sachse optical urethrotome. A good result was obtained in 70% of patients, whether a catheter had been left in for 7 or for 28 days. The urinary flow rate and a subjective assessment of his stream by the patient were found to be a reliable guide to the eventual outcome. Visual urethrotomy should be tried whenever possible before considering urethroplasty.

Internal urethrotomy has been used in the treatment of urethral strictures for at least 2 centuries since silver catheters were first armed with a concealed lancet. Civiale devised his urethrotome in 1817, and this was improved upon by Maisonneuve, who adapted it, in 1848, to screw onto a filiform guide, and later still by Otis, who added an expanding dilator (Attwater, 1943). Internal urethrotomy with the Maisonneuve or Otis instrument became part of the normal practice of urology, but it was never thought that it would cure the patient:

"Internal urethrotomy is an operation of choice, not of necessity, and by itself does not cure. It must be followed by full-sized bougies at regular intervals . . . for the remainder of the patient's life." (Loughnane, 1948)

No urologist was in doubt that urethrotomy could make an unmanageable stricture manageable, but it was never considered capable of producing a lasting cure. Hence it was with the greatest scepticism that surgeons who were brought up on the classical internal urethrotomy read the results claimed for internal urethrotomy performed under vision with the newer cold-knife optical urethrotomes (Matouschek, 1978). In a series of more than 540 strictures studied over the last 16 years at The London Hospital and St Peter's Hospital, no fewer than 110 men had undergone internal urethrotomy on one or more occasions, and all of them still needed regular bouginage, or had come to urethroplasty (Blandy, 1980). Prejudiced from this experience, therefore, we examined our results with the new Storz cold-knife optical urethrotome.

(1) Retrospective Study

Patients and Methods

A retrospective review was carried out of the first 50 patients treated with the optical urethrotome, and followed for a period of 7 to 27 months (mean 17 months). Previous dilatations had been performed at intervals from 1 to 6 months in 38 patients (76%). The age range (Fig.) was from 21 to 84 years and more than 60% were over the age of 50 years. The aetiology of the strictures (Table 1) encompassed the usual variety of causes, but it is relevant to note that urethrotomy was

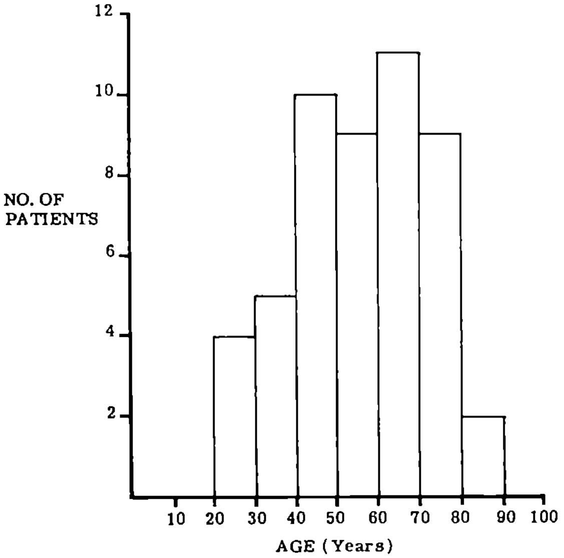

Fig. Age distribution.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Aetiology

Trauma	7
Infection	6
Prostatectomy	10
Unknown	20
Stricture after previous urethroplasty	7
Total	50

used in 14% of the cases for restenosis after previous urethroplasty of one type or another. The sites of strictures (Table 2) reflected the usual incidence of urethral stricture, and the length of history was similarly variable, from 2 months to more than 60 years.

Visual internal urethrotomy was performed with the Storz-Sachse cold knife optical urethrotome, using the 0° telescope. In most cases a ureteric catheter was passed through the stricture before it was incised. A 22 Ch silicone rubber catheter was left in the urethra, in this preliminary series, for varying periods of time, from 1 to 28 days (mean 6 days). The patients were followed with serial flow-rates, an assessment of their subjective symptoms, and by further endoscopy, urethrography, and calibration when it seemed to be indicated.

A subjective response was regarded as *good* if the patient maintained a good strong flow, *fair* when he thought it was improved but bouginage was performed again, and *bad* when there was no improvement at all and further treatment had to be undertaken.

Results

A total of 67 urethrotomies had been performed in these 50 patients, once in 35 men, twice in 13, and 3 times in the remaining 2. A good subjective result was achieved in 35 patients (70%): it was only fair in 12 men (24%) and it was bad in 3 (6%)—in the 3 latter patients there had been a previous urethroplasty of some form: 2 still attend for regular bouginage and the third has had a revision of his urethroplasty.

Table 2 Site of Stricture

Anterior	7
Anterobulbar	7
Bulbar	31
Membranous	5
Total	50

Strictures in the anterior and membranous urethra did best of all. The best results from a single urethrotomy were found in strictures that had never been treated before, but even in those of long duration, good results were still obtained after a second or third urethrotomy. Nor did it signify that there was more than one stricture: in 7 of 9 multiple strictures a single urethrotomy gave a good result. Long strictures did as well as short ones.

There was a good correlation between the patient's subjective response and his measured flow-rate, and when flow-rates were less than 15 ml/s patients were usually dissatisfied with the result. It may be noted that the mean age of those with the bad flow rates was 64 years, compared with 46 for those with good flows after urethrotomy.

When the stricture was caused by previous infection, or when its cause was not known, only a single urethrotomy was needed in the majority of patients (80%): 30% of those that followed prostatectomy or trauma needed more than a single incision, and the results were worst of all after previous urethroplasty.

It seemed possible to predict as early as 3 months after the urethrotomy whether or not the patient was going to do well: by this time 80% of those who continued to do well had a good flow and a good subjective response. In the relatively short follow-up of this series, recurrence seemed to take place early and it seemed that very few patients deteriorated after 6 months.

Complications (Table 3) were minimal: blood transfusion was never needed, infections were all of short duration, and only one patient who had a significant pyrexia had rigors. The one patient with marked extravasation had a good response and has maintained a good flow-rate since the urethrotomy.

From these results one question remained outstanding: we did not know how long to leave in the catheter after urethrotomy and from this retrospective study we could see no difference be-

Table 3 Complications

Bleeding	6
Extravasation	1
Infection urine	4
Epididymitis	1
Pyrexia (38°C)	6
Bladder spasm	4

tween the result in those who had the catheter left in for 1 week or 4. A prospective study was undertaken to answer this question.

(2) Prospective Study

Patients and Methods

Twenty-one patients entered this study and were randomly allocated to one of 2 groups according to whether a 22 Ch silicone rubber catheter was left in the urethra after urethrotomy for 7 or for 28 days. The follow-up was, as before, by flow rate measurement, assessment of the patient's subjective response, and by urethrography and calibration when indicated. In 6 patients a special type of urethrography was also performed in the hope that an objective technique could be devised that would measure the effects of urethrotomy without the usual observer error.

In this method, water-soluble contrast medium was instilled into the urethra at a recorded pressure using a small balloon catheter. Measurements were then made of the maximum diameter of the urethra and of the site of the stricture, before and after urethrotomy. The diameter of the stricture was expressed as a proportion of the diameter of the urethra in order to avoid errors arising from differences in magnification.

Results

There were no differences in the results of the 2 groups (Table 4). It made no difference whether the catheter was left in for a long or a short time.

Unfortunately, the objective method of measuring the calibre of the urethra with the urethrogram was frustrated by the unexpected discovery that there was in fact a very wide range of pressures at which the external sphincter opened and that this opening pressure was unrelated to the stricture. The opening pressure did reflect the age of the patient—the older the patient the lower the pressure needed to open the external sphincter. This made it impossible to arrive at a standard constant pressure that would suit all patients in the study and at the same time obtain a satisfactory urethrogram.

Table 4 Effect of Duration of Catheterisation

	7 days	*28 days*
Good	80%	70%
Fair	20%	30%
Bad	0%	0%

Discussion

The traditional method of treating urethral strictures by intermittent dilatation, supplemented from time to time by blind internal urethrotomy, gives a surprisingly high rate of complications—in one series of 141 strictures managed only by this combination of methods no fewer than 51% were found to have had one serious complication or another (Blandy, 1980). The present study confirms the results reported from other centres, that internal urethrotomy under direct vision can offer very definite and sometimes (in the limited duration of the present follow-up) long-lasting benefit. The criteria for success in previous reports, as well as the details of the technique, have varied greatly. Catheters have been left indwelling for varying periods of time, self-dilatation by voiding against the penis held closed by the hand has been advised and some authors have used steroid instillations (Smith *et al.*, 1979; Gaches *et al.*, 1979; Renders *et al.*, 1979).

The present study suggests that the urethrogram cannot be used as an objective measure of the success of the urethrotomy, since it depends so much on the varying opening pressure of the external sphincter. Calibration with instruments is notoriously fallacious, since it is quite impossible to pass a bougie without to some extent performing a dilatation. Of all measures, the patient's flow-rate, which is closely reflected in his own assessment of the result, seems to offer a useful guide to the success or failure of the operation.

Clearly any method for treating stricture of the male urethra must be ratified by time, since the natural history of urethral stricture is measured in decades, not in months. Nevertheless, the promising results of this relatively small series, observed for periods of up to 27 months, have obliged us to change our opinion and to offer a modified welcome to visual urethrotomy. It appears to be a very useful addition to the urologists' armamentarium and it should certainly be tried, perhaps on several occasions, before resorting to urethroplasty.

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The Use of Thioglycolic Acid in Hair-bearing Skin Inlay Urethroplasty

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Summary—Thioglycolic acid, in commercially available spray, lotion or cream, was used to remove the hair from the scrotum, pubis and perineum in 45 patients, with minimal discomfort in only 11 patients and wound infection in only one. Eighty-five per cent of these patients said they preferred the depilatory cream to the routine pre-operative shave with a razor. In 3 of 4 patients where it was instilled intraurethrally to remove hairs from skin-inlay urethroplasties it was successful in removing hairs; in the fourth patient most of the hairs were removed. None of these patients had anything more than a short-lasting irritation afterwards.

It was the search for something better than lime, traditionally used to remove hair from hides, that led to the discovery of the depilatory properties of the aliphatic mercapto acids, of which group thioglycolic acid (Fig. 1) is a member (Turley and Windus, 1934; Smith, 1946). They act on the keratin of hair by breaking the disulphide bond that conjugates the amino acid cystine, itself an important constituent of keratin (Fig. 2). After rupture of these disulphide bonds there is an increase in the osmotic pressure within the hair fibre and it swells, becomes weak, and finally breaks off, usually at its base. The chemical reaction does not affect the hair follicle, and the end of the hair is softly rounded rather than chisel-shaped as it is after conventional shaving with a razor. The natural oil of the skin protects its surface keratin from the action of the thioglycolic acid, but allergic reactions may occur, as they may from any chemical applied to the skin. Extensive animal studies have been carried out (Lehman, 1949; Freeman *et al.*, 1956; Prigot *et al.*, 1962) and commercial preparations are in everyday use by women who want to rid themselves of unsightly body hair. Most of these use the calcium salt of thioglycolic acid in an alkaline medium.

In surgical practice Powis *et al.* (1976) advocated one of these commercial preparations in the pre-operative skin preparation of 46 patients, but did not use it in the perineal or scrotal region. The preparation which they studied is no longer commercially available, and has been superseded by a similar product (Immac^R) used in the present study.*

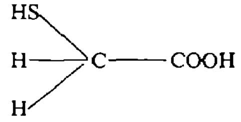

Fig. 1 Thioglycolic acid.

This commercial preparation is put up either as cream, lotion or spray, in a 4.5% w/w concentration having a pH 12 to 12.5. Repeated attempts were made to culture micro-organisms from these preparations and always with sterile cultures.

In preliminary studies with volunteers, it was noted that no untoward skin reactions took place when the cream was applied to depilate the scrotum.

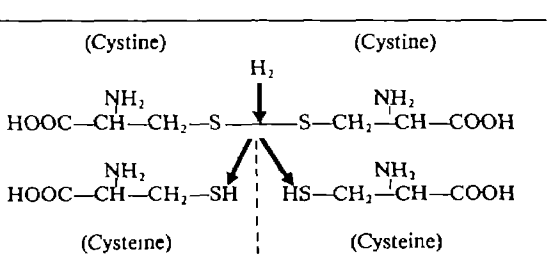

Fig. 2 Action of thioglycolic acid on keratin.

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*Immac^R is a product of the International Chemical Company Ltd.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980

Patients and Methods

Depilation of the Scrotum and Perineum with Thioglycolic Acid

In 45 patients whose informed consent had been obtained, a preliminary patch test was carried out at least 12 h before the application of the thioglycolic acid in a spray or lotion base. An area approximately 2 × 2 cm was covered with the cream for 10 min and it was then washed off. In no case was there any sign of inflammation.

After an interval of at least 12 h, the spray or lotion was applied to the pubic, scrotal and perineal region either by the patient or by a member of the staff. The thioglycolic acid was left in contact for exactly 10 min, after which the patient took his routine pre-operative bath, washing the area thoroughly to get rid of the softened and matted hair.

A questionnaire was completed by each patient in the study. Careful note was made whether or not the depilation had caused any discomfort and each patient was carefully examined for signs of skin reaction. At the time of surgery the effectiveness of the depilation was assessed by the surgeon. The operations varied from exploration of the testis to implantation of a penile prosthesis. All post-operative complications were recorded and the areas again examined at the time of the patient's discharge from hospital.

Results

Of the 45 patients treated, 33 had no irritation whatsoever: in 11 they noted a mild "hot" feeling around the scrotum which lasted for a few minutes and was never unpleasant. In one patient, who in retrospect thought he had probably not washed thoroughly in the creases of his groins, there was some irritation in the inguinal skin crease lasting 18 h—but even this was not sufficient to make him lose sleep.

All of the hair was removed in 66% of the patients: in 22% there were a few unimportant hairs left at the edge of the prepared region, and in none of these had the application been done by a member of the medical or nursing staff. One patient had a brief wound infection but no sign of irritation of the skin.

Twenty-six of these patients had previously undergone the standard pre-operative razor shaving of their pubic and scrotal hair: of these, 22 (85%) preferred the thioglycolic acid; only 4 patients said they preferred the shave because it was less "messy".

Thioglycolic Acid in the Management of Hair Growing in Skin-inlay Urethroplasties

The excellent results obtained in the use of thioglycolic acid in pre-operative preparation of the skin of the perineum and scrotum led to the concept that it might be used in ridding hair from patches of skin taken from the scrotum and put into the urethra.

The need for such treatment does not arise very often. In a series of 321 skin-inlay urethroplasties observed for periods of up to 16 years only 11 patients needed treatment for hairballs (3.4%); nevertheless it is recognised that concretions forming on hair in the urethra can cause irritation, harbour infection, and be a source of real, if unusual symptoms.

Intraurethral Thioglycolic Acid

In volunteers the standard commercial concentration of thioglycolic acid was placed in the mouth and the urethra for periods of 10 to 30 min. In the urethra the application for 20 min of the lotion produced discomfort on voiding that lasted for 24 h and caused some oedema of the mucosa visible in the navicular fossa, but by 36 h all evidence of irritation had disappeared. There were no systemic reactions and no late complications. Similar results were obtained with instillation into the mouth and into the urethra for shorter periods.

Suitable patients who needed this treatment were few, and thioglycolic acid was used in only 4 patients who had variously thick crops of hair visible on endoscopy, or had formed actual hairballs. The thioglycolic acid was inserted at the time of the urethroscopic assessment, under a general anaesthetic. Care was taken to fill the bladder with 100 ml water at the time of the preliminary urethroscopy. The urethra was then filled with an appropriate volume of the thioglycolic acid lotion and a penile clamp was applied for 10 min exactly. The urethra was then repeatedly washed out and the urethroscopy was repeated.

Results

All of the hairs were dissolved in 3 patients, and in the fourth only a few hairs remained. In 2 with hairballs, the stones fragmented and were easily removed by irrigation: in the third a matted hairball seemed to be considerably softened and was easily lifted out of the urethra with the biopsy forceps. No patient suffered any systemic reaction. Only one observed any irritation after 12 h, and this had gone by 24 h.

Discussion

Any substance instilled into the urethra may be absorbed, and therefore it is clear that the utmost caution must be followed when using thioglycolic acid. Fortunately the need is likely to be very infrequently encountered, for hairball formation is a relatively rare complication of skin-inlay urethroplasty. Nevertheless, when faced with the alternative of performing perhaps a traumatic and difficult extraction of a hairball stone from a urethra, or attempting to soften and dissolve it first with thioglycolic acid, the latter would seem to commend itself as the lesser and safer of the 2 procedures. Experimental studies where thioglycolic acid has been placed in the body cavities of laboratory animals (Freeman *et al.*, 1956), supplemented by the very widespread commercial use of the preparations that are sold over the counter, suggest that it is relatively safe.

No doubt the use of thioglycolic acid in the urethra will have a very limited application, but in the routine preparation of patients for perineal or scrotal surgery it can be thoroughly recommended, since it offers the surgeon a hair-free smooth and unscarified skin, free from those small abrasions that invite post-operative infection, and at the same time it offers the patient an escape from a most uncomfortable and sometimes painful experience.

Acknowledgement

We are grateful to Mr A. W. Titley, Marketing Director of International Chemical Company Ltd (Wrafton, Braunton, Devon) for his advice and for supplying the depilatory agents used in this study.

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Primary Carcinoma of the Female Urethra

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Summary—Experience in the diagnosis and management of 39 female patients with primary carcinoma of the urethra is described. The condition presents to both gynaecological and urological units and has a relatively good prognosis provided that it is diagnosed quickly. There must be, however, a clinical awareness of the condition in those patients presenting with non-specific urological symptoms.

Radiotherapy is the treatment of choice using interstitial implants for the superficial tumours and external beam for the deeper tumours. Surgery alone is possible in only a small number of cases, it being reserved mainly for recurrent or resistant disease.

Primary urethral carcinoma in the female is rare, accounting for less than 0.02% of malignant disease in women (Grabstaldt *et al.*, 1966). There are thus only a few reports on the diagnosis, staging and management of significant numbers of cases.

The experience gained from 39 patients seen and treated over a period of 30 years is presented. Diagnosis and staging and the influence of these on management is discussed.

Patients and Methods

During the period 1949 to 1979, 39 female patients with primary carcinoma of the urethra were seen and treated at The Royal Marsden Hospital.

This condition occurred mainly in the older patient. The ages at presentation ranged from 42 to 85 years and 59% were aged 60 years and over (Fig. 1), an observation also noted in other series (Riches and Cullen, 1951; Staubitz *et al.*, 1955; Grabstaldt *et al.*, 1966; Pointon and Poole-Wilson, 1968).

Presenting symptoms could be divided into:

Gynaecological

(1) Bleeding—Bright red blood was often noticed, the origin of which patients found difficult to determine.

(2) Lump or ulcer—An awareness of an abnormality in the vulval/vaginal area.

Urological

These were non-specific symptoms—urinary frequency, difficulty and pain on micturition, occasionally urinary retention.

Metastatic

Local inguinal lymphadenopathy.

Diagnosis and Staging: All patients were submitted to EUA, cystoscopy and biopsy. There have been several staging systems described (Whitehouse, 1911; Grabstaldt *et al.*, 1966; Pointon and Poole-Wilson, 1968) but the modification of Chau (Chau and Green, 1965; Taggart *et al.*, 1972) has recently become widely used and accepted. The stages defined are:

Stage I Disease limited to the distal one-half of the urethra.

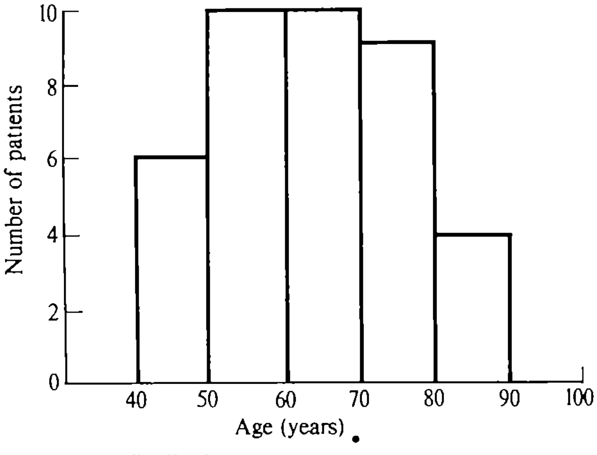
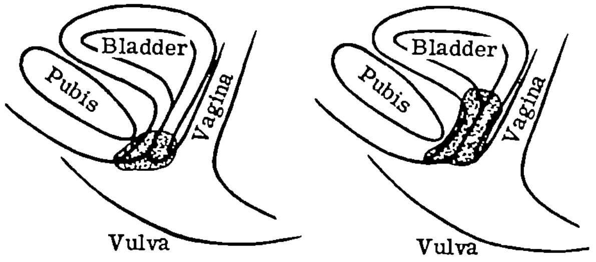


Fig. 1 Age distribution.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.



Stage I

13 cases

Stage II

7 cases

Fig. 2

- II Disease involving the entire urethra, with extension to the periurethral tissues, but not involving the vulva or bladder neck.
- III (a) Disease involving the urethra and vulva.
  - (b) Disease invading the vaginal mucosa.
  - (c) Disease involving the urethra and bladder neck.
- IV (a) Disease invading parametrium or paracolpium.
  - (b) Metastasis:
    - (1) Inguinal lymph nodes
    - (2) Pelvic nodes
    - (3) Para-aortic
    - (4) Distant

Diagrammatically, these can be seen in Figures 2 to 4 with the numbers of cases presenting at each stage.

Treatment: The selection of treatment by radiotherapy or surgery or a combination of both depended on clinical stage rather than histological type.

Radiotherapy: This was by either external beam or interstitial implant or both.

Interstitial Implant: Tumours that were easily accessible. Stages I, III(a) were amenable to interstitial implantation.

External Beam: Tumours that were deeper or too large for implants were treated by external beam. It was also used in combination with implantation, thus increasing the tumour dose.

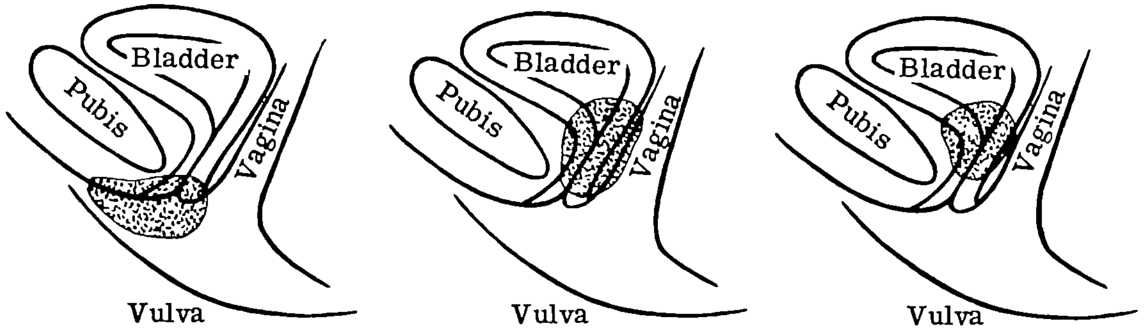
Surgery: Surgery varied from local excision to anterior exenteration. It was used as the definitive treatment or in combination with radiotherapy as treatment for resistant or recurrent disease.

Results

Those tumours that were superficial, Stages I and III, presented with mainly gynaecological symptoms (Table 1) whereas the deeper or more extensive tumours, Stage II, some of Stage III and Stage IV, presented with mainly urological symptoms. Only 2 patients (5%) presented with metastases.

Biopsy was performed on all cases (Table 2). There was an unusual ratio of squamous cell tumours to transitional cell tumours in this series, there being usually a predominance of squamous cell tumours. The reason for this discrepancy is unclear. There was also a large number of malignant melanomata.

As the urethra is lined by squamous cell epithelium in the distal two-thirds and by transitional cell epithelium in the proximal one-third, histopathology of the tumours should be related to site



Stage III a

6 cases

Stage III b

5 cases

Stage III c

2 cases

Fig. 3

Table 1 Presentation by Stage

Stage	*Cases*	*Presenting symptoms*			
		Gynaecological	*Urological*	*Mixed gynaecological + urological*	*Urological + metastases*
I	13	12	—	1	—
II	7	4	2	1	—
III	13	7	3	3	—
IV	6	—	3	1	2
Total	39	23 (59%)	8 (21%)	6 (15%)	2 (5%)

of occurrence (Table 3). Squamous cell tumours presented mainly at Stages I and III(a). Transitional cell tumours tended to be deeper tumours, presenting at Stages II, III(b) and IV. Of the 5 transitional cell tumours that presented at Stage I, 3 were pedunculated.

The treatment depended on clinical stage rather than histology (Table 4). The superficial tumours, Stage I and III especially, were amenable to interstitial implantation and 17 patients were treated this way with and without additional therapy. The deeper and more extensive tumours were treated by external beam therapy.

Surgery alone was possible in only a small number of cases. This was local excision for Stage I and anterior exenteration in the more advanced cases. When combined with radiotherapy, surgery depended on the volume and site of the residual or recurrent disease. If small and amenable to local surgery then this was usually performed. If, however, the disease was more extensive, then anterior exenteration was performed.

Survival could be related to both histological and clinical stage. With the exception of malignant melanoma, the 5-year survival was between 45% for squamous cell carcinoma and 65% for transitional cell carcinoma (Fig. 5). All patients with malignant melanoma died within 2 years.

Excluding malignant melanoma, with its poor prognosis, and relating survival to Stage: Stage I and III have a similar survival rate whereas Stage II and IV have a poor prognosis (Fig. 6).

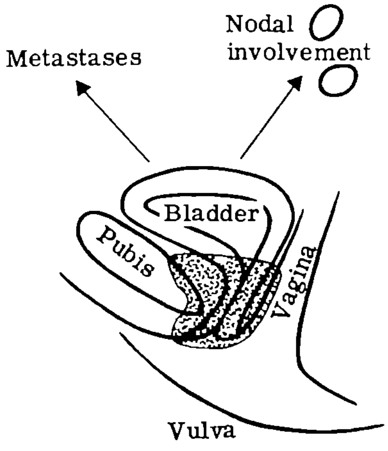
Table 2 Histology

Squamous cell carcinoma	13
Transitional cell carcinoma	12
Anaplastic	3
Adenocarcinoma	4
Malignant melanoma	5
Lymphosarcoma	1
Hodgkin's disease	1

Discussion

Carcinoma of the urethra may present to either gynaecological or urological units. A lesion at the external meatus (Stage I) or involving the adjacent vulva (Stage III(a)) presenting with gynaecological symptoms is easily recognised clinically. These tumours are mainly squamous and 84% of these tumours presented within three months of the onset of symptoms (Table 5).

Stage II and Stage IV lesions, usually transitional cell tumours, present with predominantly urological symptoms which are rather non-specific. There may be nothing obvious on superficial examination, diagnosis being made on EUA and



Stage IV

6 cases

Fig. 4

Table 3 Stage at Presentation by Histology

Stage	*Squamous cell carcinoma*	*Transitional cell carcinoma*	*Anaplastic*	*Adeno-carcinoma*	*Malignant melanoma*	*Others*
I	2	5	1	2	2	1
II	3	2	—	—	1	1
III(a)	5	—	1	—	—	—
(b)	1	1	1	1	1	—
(c)	1	—	—	1	—	—
IV(a)	—	2	—	—	—	—
(b)	1	2	—	—	1	—
Total	13	12	3	4	5	2

cystoscopy. This is reflected in the delay in diagnosis of transitional cell tumours compared with squamous cell tumours, only 42% having their symptoms for less than 3 months. The delay may also contribute to the poor prognosis of Stage II and IV tumours. With a clinical awareness of the potential diagnosis the results of this group may be improved.

Treatment should be aggressive and related to clinical stage rather than histological type. Radiotherapy is the treatment of choice with surgery retained for recurrent or resistant disease. Stage I and Stage III(a) lesions are amenable to interstitial irradiation, which is the treatment of choice (Chau and Green, 1965; Pointon and Poole-Wilson, 1968; Prempree *et al.*, 1978). It can be supplemented with external irradiation or surgery. External beam therapy is used for the deeper tumours, Stage II, III(b), (c) and IV. Surgery alone is possible in only a small number of cases, which is in agreement with other series (Grabstaldt *et al.*, 1966).

Even if the tumour has spread to the adjacent vulva, prognosis is still good (60% 5-year sur-

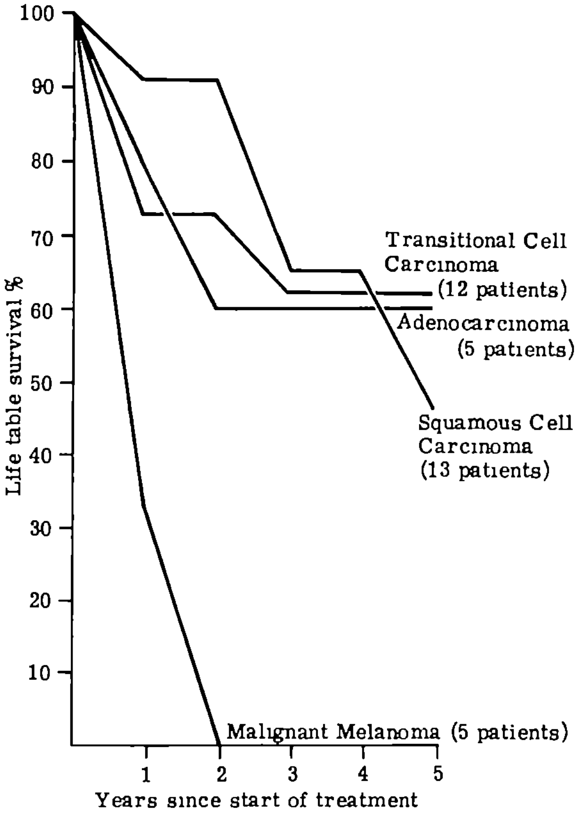


Fig. 5 Carcinoma of the urethra—survival of histology.

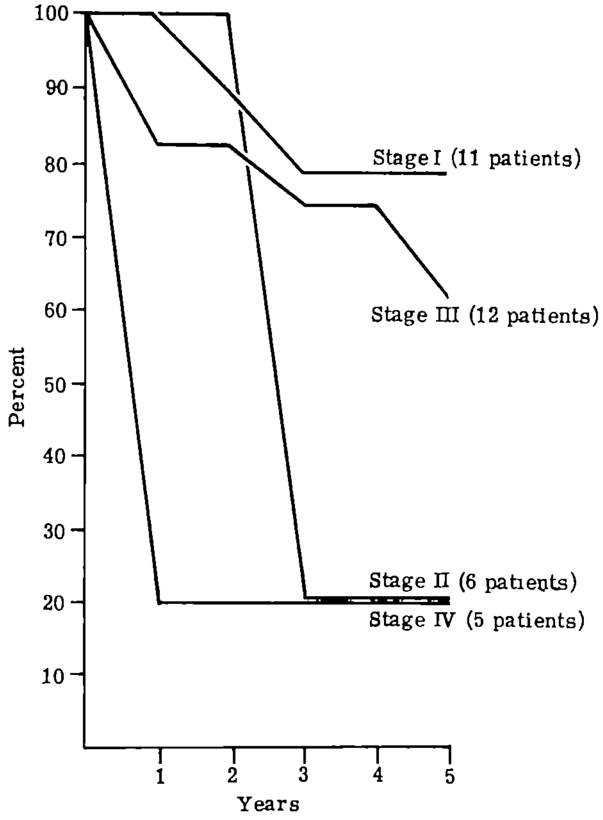


Fig. 6 Survival by stage excluding malignant melanoma.

Table 4 Treatment by Stage

Stage	*Radiotherapy*					
	Interstitial only	*Interstitial + external*	*Interstitial + surgery*	*External only*	*External + surgery*	*Surgery alone*
I	5	2	—	—	1	5
II	1	2	—	3	1	—
III	2	3	2	4	1	1
IV	—	—	—	5	—	1
Total	8	7	2	12	3	7

Table 5 Delay in Presentation by Histology

Symptoms→diagnosis	*Squamous cell carcinoma*	*Transitional cell carcinoma*	*Anaplastic*	*Adeno-carcinoma*	*Malignant melanoma*	*Others*
<1 month	5	1	1	1	1	1
1-2 months	2	3	—	—	2	—
2-3 months	3	1	—	2	1	—
3-6 months	—	2	2	—	—	—
6 months-1 year	1	3	—	—	1	—
1-2 years	1	—	—	—	—	—
2-3 years	—	2	—	—	—	1
Total	12	12	3	3	5	2

2 cases—duration of symptoms unknown: 1 adenocarcinoma and 1 squamous cell carcinoma.

vival). This is in agreement with Prempree *et al.* (1978) but against the findings of Chu (1973) who reported that such cases in his experience had a poor survival.

As stated previously, there have been several staging systems and there is as yet no TNM system for the urethra. The initial classification was that of Whitehouse (1911) who divided the tumours into 2 groups, vulvo-urethral and urethral. This was later extended by Pointon and Poole-Wilson (1968) to 3 groups, urethral orifice, vulvo-urethral and urethral. Chau and Green (1965) later defined 4 stages based on treatment techniques: (1) Anterior urethra which included disease extending into the vulva. (2) Posterior urethra including tumours involving the bladder neck and trigone. (3) Entire urethra—an extensive tumour, the site of origin within the urethra being difficult to define and including ulceration into the vagina. (4) Entire urethra and metastases including tumours that have involved the adjacent parametrium as well as those that have metastasised.

This system was later modified on anatomical grounds by Taggart *et al.* (1972) and later by Prempree *et al.* (1978) to the one most widely used at present. The relationship between the original and modified system is seen in Table 6. From our experience the original Chau classification is easier to use for both treatment policy and disease prognosis. For this reason perhaps the original classification should possibly be used rather than the modification.

Table 6

Original Chau classification	*Equivalent stage on modified system*	*Treatment selection*	*Prognosis in this series*
Anterior urethra	I + III(a)	Surgery or interstitial implant	Good
Posterior urethra	III(b) + III(c)	External beam	Fair
Entire urethra	II	External beam	Poor
Entire urethra + metastases	IV	Palliative	Poor

Primary malignant melanoma is very rare. In the case reports published, the prognosis is universally poor (Block and Hotchkiss, 1971). Our series of 5, a relatively large number, also had a very poor prognosis. They presented at all stages despite 80% being diagnosed within 3 months of the onset of symptoms. Treatment was either surgical or radiotherapy with, in all cases, subsequent chemotherapy. Despite adequate local treatment, the disease disseminated very rapidly.

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Late Sequelae of Hypospadias Repair

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Summary—Twenty-three cases are reported in which serious late sequelae of previously repaired hypospadias led to difficult technical problems in repair. Chordee, rotation and fistulae often complicated persistent strictures. To avoid the risk of fistula when operating upon previously scarred penile skin, a method of repairing or replacing the diseased anterior urethra is described, based upon the principles of the dartos pedicle island patch.

The little boy born with hypospadias usually has the deformity corrected before he goes to school at the age of 5 or 6 and with modern methods of one-stage or two-stage repair, a good result can usually be obtained in terms of the correction of chordee and the reconstruction of the distal urethra (Hodgson, 1978) when evaluated at this age. Not all children in the past have been so fortunate and when things have gone wrong after previous attempts to correct the hypospadias, an adult may present himself for treatment with a combination of problems that defy conventional methods of treatment. The usual late sequelae of such management include one or more of the following complications: an uncorrected or relapsed chordee, an uncorrected rotational deformity, one or more fistulae, and a variety of urethral strictures ranging from a tight distal stenosis to strictures of the whole length of the adult urethra probably dating from periods of catheterisation in childhood.

To correct these complications and deformities it is not possible as a rule to employ the techniques commonly used in the boyhood hypospadias and, in particular, it is seldom possible to make use of any spare foreskin, since it will have been used up in the previous attempts at repair. On occasions the only choice is to fashion an entirely new urethra. Because this presents a certain technical challenge and because we believe that the island patch on a dartos pedicle can be adapted to meet this challenge, we have reviewed our experience and describe the technique and its complications.

Methods and Material

We reviewed 23 patients, their ages ranging from 9 to 67 years, only 2 of them being under 17 (mean age 37 years). All had undergone various forms of treatment previously. Their symptoms differed: 17 complained of a poor stream; 12 found their deformed penis, either because of its curvature or its rotation, to be an embarrassment, and in 3 patients difficulty with intercourse was the main complaint. In 5 there were, in addition, symptoms of burning and frequency.

A urethral stricture was present in 17 patients (Table 1). Twelve had severe residual chordee. In 2 the uncorrected rotational deformity led to embarrassment. In 10 there were one or more fistulae opening on to the ventral aspect of the penis. One man presented, 24 years after he had undergone a hypospadias repair by Sir Denis Browne, with a hairball calculus in the distal skin-lined urethra.

One of the striking features of this series was the delay between the apparently successful initial operation and the onset of the symptoms that brought the man to hospital: the interval varied from 5 to 50 years, but in most instances it appeared that a successful operation done in child-

Table 1 Late Sequelae of Hypospadias Repair

Stricture	17
Hairball-stone	1
Chordee	12
Torsion	3
Fistulae	10
Obstructive uropathy	2
Renal calculus	2

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 2 Late Sequelae of Hypospadias Repair: Methods of Repair

Meatoplasty	2
2-stage scrotal flap	5
Swinney-Johanson	2
Island patch, 1-stage	5
Repair of fistulae	3
One-stage tube	6

hood had remained satisfactory until adolescence, when growth of the new urethra failed to keep pace with the enlargement of the penis.

Surgical Correction (Table 2)

In many of these patients it was not difficult to put the trouble right. For those with simple rotational deformity, the penile skin was circumcised, slid back, and sewn up after rotating the penis to the correct position. Small fistulae alone presented no problem, but often they were associated with persistent distal stenosis. The hairballs were removed endoscopically. The most difficult cases were the men with multiple scars of old operations on the penis, with severe chordee, several fistulae, and little skin to spare. Any incision through the previous sites of surgical repair would risk subsequent fistula formation. The foreskin was never available for use in the repair.

Presented with this problem the following procedure has been used, with individual variations according to the individual operative findings in each patient.

First, access to the distal penis and urethra is obtained by sliding back a complete sleeve of penile skin after circumcising at the level of the usual site for circumcision (Fig. 1). There are always many tough adhesions tethering the skin to the corpora cavernosa. In most cases the narrow and short strip representing the previous urethra is not worth conserving and should be dissected away completely (Fig. 2) up to the healthy proximal corpus spongiosum. Even this may need to be dissected more proximally if the chordee is to be corrected completely. To check whether or not the chordee is fully corrected, saline is injected into the shaft of the penis after placing a tourniquet on its base. All of the fibrous tissue tethering the corpus spongiosum to the distal part of the corpus cavernosum on each side needs to be divided and dissected away.

The next problem is how to bridge the gap. Fortunately in all of these patients it has been possible to find plenty of redundant scrotal skin. Using a 24 FG bougie as a guide and using a tin-

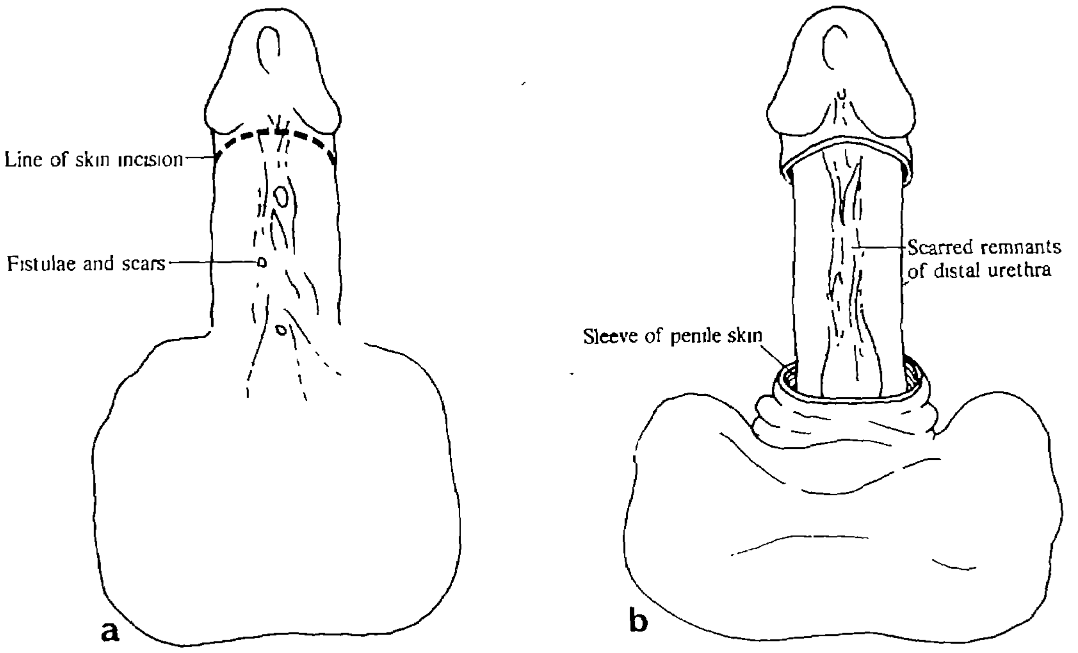

Fig. 1a, b To avoid the previously operated on skin of the penis, access to the urethral remnant is obtained by sliding the penile skin back as a sleeve.

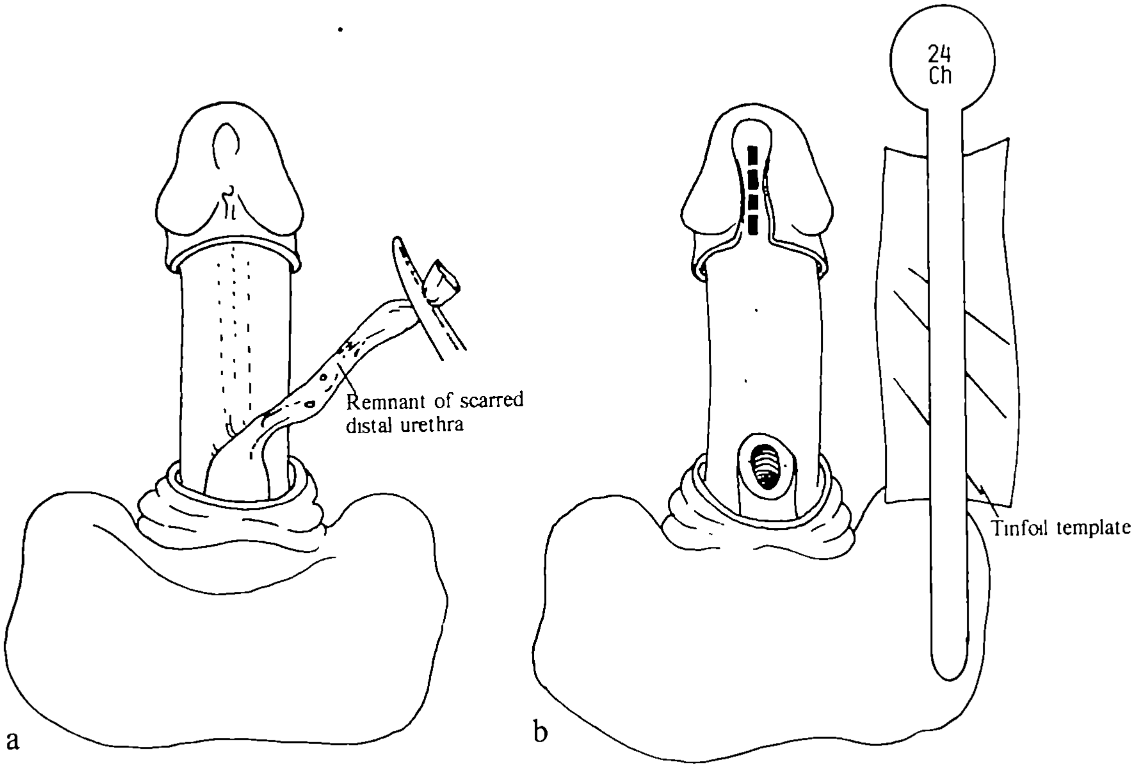

Fig. 2 (a) Severely scarred and contracted distal urethral tissue is dissected away until, (b) healthy proximal urethra is found.

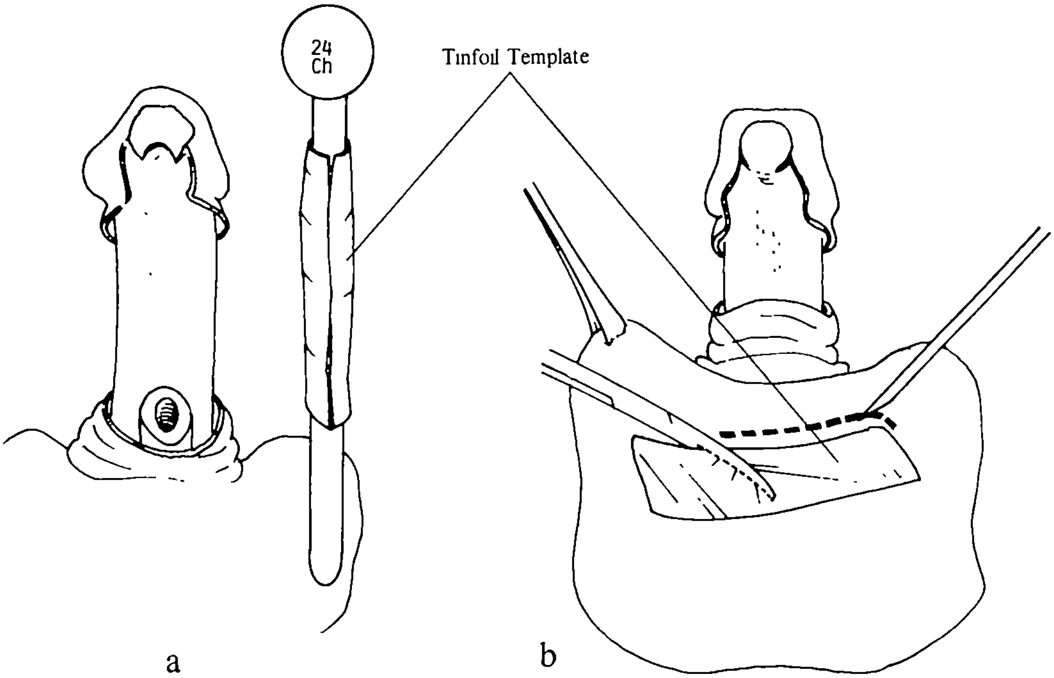

Fig. 3 Using tinfoil from a catgut packet, a skin island is marked on the scrotal skin with methylene blue.

foil template and methylene blue (Fig. 3) the strip of skin that will be used to form a complete tube is marked on the scrotum.

This strip is then formed into a dartos pedicle island patch (Fig. 4), using the dartos to one side of the scrotum or the other, undermining the skin of the scrotum in the usual way and taking care not to injure the small blood vessels running in the pedicle of the dartos.

The skin is now sewn into the shape of a tube and the tube drawn under the penile sleeve (Fig. 5). One end is sutured to either the glans penis or to the distal urethra if this is still present and is of adequate calibre. The proximal end is sutured to the spatulated proximal urethra. The skin tube is splinted with a 16 FG silicone rubber Foley catheter (Fig. 6).

The sleeve of penile skin is then drawn back to cover the new urethra and sutured in its previous position (Fig. 7). The catheter remains in position for 2 weeks.

Modifications of this Method

In 5 patients it was not necessary to reconstruct the entire distal urethra. In one of the adult men, born with a glandular hypospadias that had only

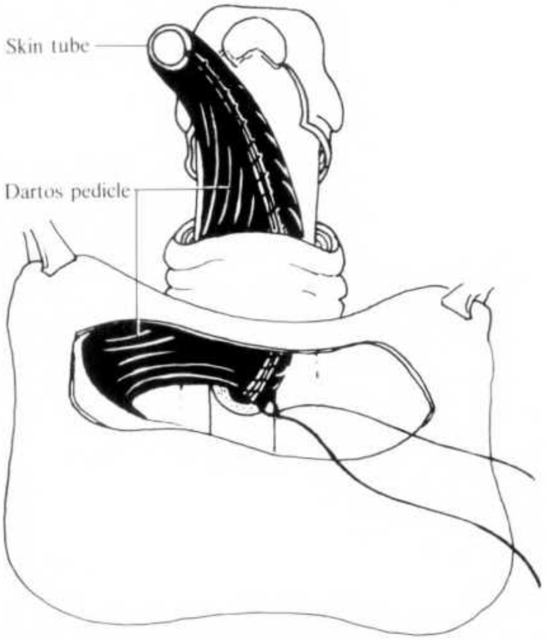

Fig. 5 The dartos pedicle island patch is formed into a tube with the surface of the skin on the inside: the tube is drawn up under the sleeve of penile skin.

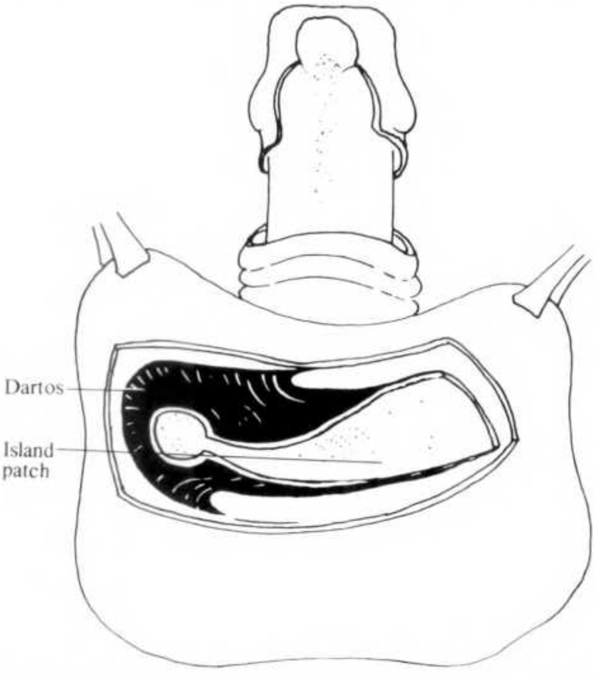

Fig. 4 An isolated island patch of skin with its own pedicle of dartos is made by developing the plane between skin and dartos. The base of the pedicle should be to one or other side.

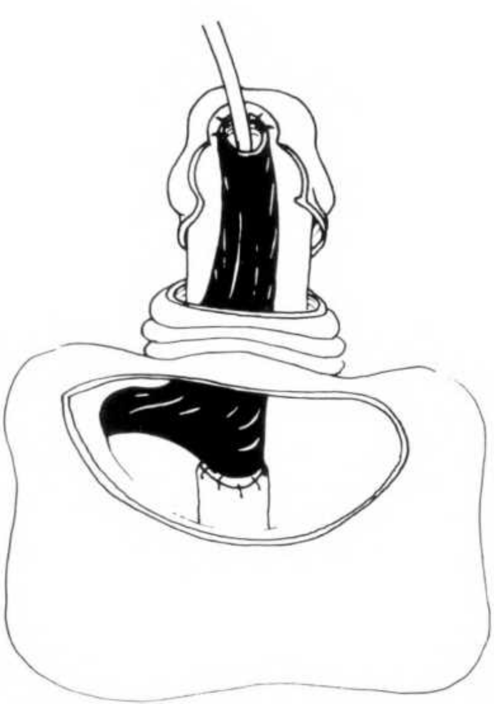

Fig. 6 One end of the tube is sutured to the glans, the other to the proximal (healthy) urethra, over a splinting catheter.

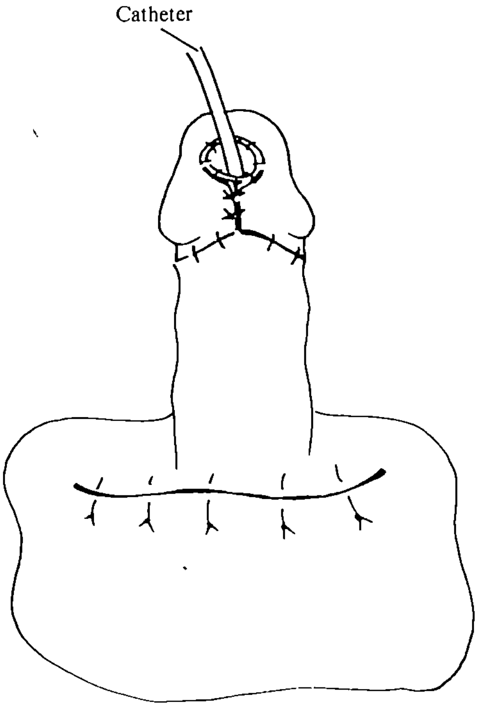

Fig. 7 The penile skin sleeve is drawn up and stitched back into its original position and the defect in the scrotum is closed.

been treated (probably) by a meatotomy in childhood, the distal 4 cm of the urethra were narrow, as if there was a hypoplasia of the distal urethra, but there was no chordee, and in 4 others a similar distal stricture was found in a partly reconstructed urethra. In these patients a narrower skin strip was formed on the dartos pedicle—less wide than the strip needed to form a complete tube, but still taken from scrotal rather than from penile skin. The strip was then drawn up and let in to the distal narrow urethra after this had been split down its ventral midline.

Results

The follow-up of these patients has ranged from 2 to 4 years. In 2 of them recurrent strictures have developed, in one after a formal urethroplasty of the classical Johanson-Swinney type, and in the other, following a distal meatoplasty. In the remainder the results in terms of sexual and urinary function have been good. One patient required reassurance when he observed hairs growing from the meatus and has been offered thioglycollic acid to treat these hairs.

Urethroscopy of the new distal urethra presents an unusual appearance, since it is apt to be folded and tortuous unless particular care is taken to draw the penis out straight. For the same reason blind instrumentation should be avoided, since the new urethra, being made of skin, offers a very unusual sensation to the fingers guiding the instrument. It is safer to use a narrow endoscope with a 0° telescope and advance it under direct vision.

Discussion

This experience suggests that there may be a need to re-evaluate young patients who have undergone successful urethral reconstruction for hypospadias in childhood. The smallness of the present series, when compared with the enormous numbers of children who have undergone hypospadias repair of one type or another, makes it probable that the risk of late serious complications is only a very small one. Nevertheless, when a young adult presents with a much-scarred penis, complicated by fistulae and chordee, the surgical problem it poses is not an inconsiderable one. We believe that the method adopted here, of avoiding an incision into the penile skin and of making a new skin tube out of scrotal skin, offers a useful technique that can be modified and adapted to meet a wide variety of local problems.

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Doppler Flow Studies, Venography and Thermography in the Evaluation of Varicoceles of Fertile and Subfertile Men

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Summary—The varicoceles of 39 men of proven fertility and 57 husbands of infertile marriages were assessed by the Doppler technique and classified according to venous activity. Retrograde left renal venography in 17 subjects showed that Doppler grading was unable to distinguish between 7 patients with competent internal spermatic veins and 10 with internal spermatic vein reflux. Patients whose varicoceles were associated with internal spermatic vein reflux had a significant reduction in sperm density and these may be implicated as a cause of male infertility. The remaining varicoceles were probably the result of incompetence of other venous tributaries of the spermatic cord and were associated with higher sperm densities.

The Doppler was able to identify accurately those varicoceles with significant elevation of scrotal temperature as determined by computer assisted infra-red scrotal thermography. The sperm densities of these patients were similar to the values found in patients with normal scrotal temperatures.

The varicoceles of infertile men were found to have a greater incidence of spontaneous venous activity than the varicoceles of fertile men and this suggests that any reduction of fertility caused by elevation of scrotal temperature may be via an effect other than a reduction in sperm density.

The role of the varicocele in the aetiology of male infertility has recently been questioned (Rodriquez-Rigau *et al.*, 1978) and the results of a controlled clinical trial of internal spermatic vein ligation by Nilsson *et al.* (1979) add to the speculation. Varicoceles are found commonly in oligozoospermic men (Dubin and Amelar, 1971; Greenberg *et al.*, 1978), but there is disagreement over the physical signs of a small varicocele. The assessment of a varicocele should be based upon data related to objective phenomena which affect fertility. Venography, thermography (Comhaire *et al.*, 1976) and the Doppler stethoscope (Greenberg *et al.*, 1977) have been used to improve the accuracy of diagnosing small varicoceles and to identify subclinical internal spermatic vein reflux.

In a previous study (Hirsh *et al.*, 1980) the Doppler technique was used to evaluate spontaneous venous activity in the varicoceles of infertile men. The present study was concerned with the relationship of the Doppler findings to internal spermatic vein incompetence, scrotal temperature, sperm density and fertility.

Patients and Methods

Ninety-six men were selected from fertile volunteers, vasectomy counselling clinics and couples seen in an infertility clinic. Thirty-nine (average age 33.5 years) had fathered at least one child and 57 (average age 32.0) were the male partners of infertile marriages. All subjects had left-sided varicoceles except 2 patients with oligozoospermia (sperm densities 1.4 and 6.7 m/ml) who were investigated because subclinical spontaneous reflux had been detected during Doppler examination of their left spermatic cords. Twelve subjects without varicoceles comprised a control group for the thermography study and 6 of these were of proven fertility.

The clinical examination for a varicocele was performed with the patient standing at room

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

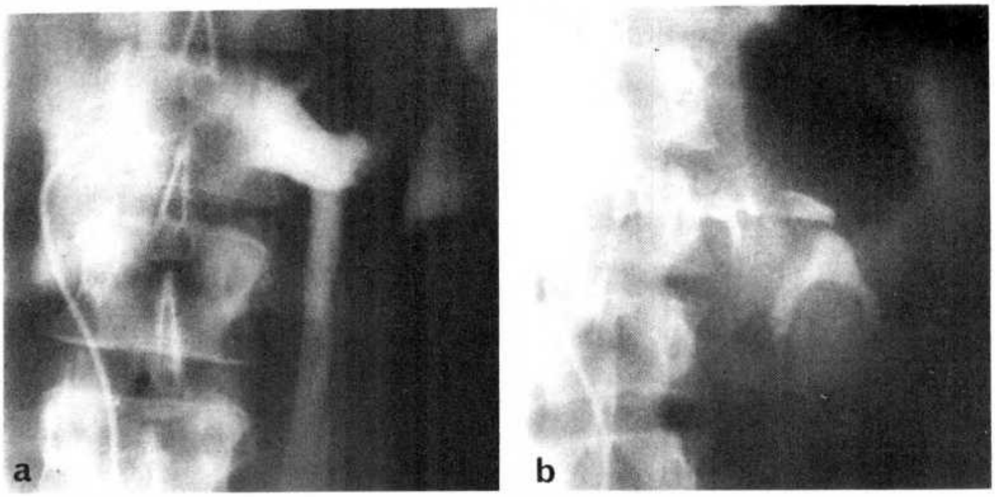

Fig. 1 Retrograde left renal venography showing (a) Internal spermatic vein reflux, (b) A competent valve preventing reflux.

temperature and under conditions of adequate illumination. The diagnosis of a varicocele was established by the presence of a visible or palpable collection of tortuous veins in the spermatic cord during quiet respiration.

The Doppler examination was then performed during normal respiration and with the patient standing. Evaluation of venous reflux was made from the audible signal of a Sonicaid Cardiovascular Pocket Unit and chart recordings produced from the zero crossing output of a Sonicaid BV 380 Directional Velocimeter coupled to an Ormed Engineering MX 212 chart recorder. Varicoceles were classified according to venous activity into stasis (grade I), intermittent reflux (grade II) and continuous reflux (grade III).

Selective catheterisation of the left renal vein was performed via the right femoral vein under local anaesthesia and 10 ml of 58% Urografin was injected by hand. The patient was screened during both quiet respiration and the Valsalva manoeuvre in both supine and 60° feet down positions. Films were taken at one-second intervals using a 70 mm camera. Care was taken to ensure that the tip of the catheter was lateral to the orifice of the internal spermatic vein and reflux was identified by the passage of contrast towards the testis in the absence of competent valves (Fig. 1).

Infra-red scrotal thermography was performed using a computer assisted thermal scanning system (IR11 Barr and Stroud Ltd) which included a Perifile 6000 tape recorder, television monitor, tracker point system and built in calculation package. The scrotum was separated from the adjacent skin of the thighs by the interposition of crepe bandages to prevent transmitted heat and the penis was held vertically by the patient. The patient was allowed to stand for 20 min in a constant temperature environment of 20°C to allow thermal equilibration to occur. Thermograms were obtained from the anterior aspect of the scrotum at a distance of 71 cm and recorded on to magnetic tape. These were later retrieved, displayed on the monitor and a template placed on the screen to overlie symmetrically the anterior

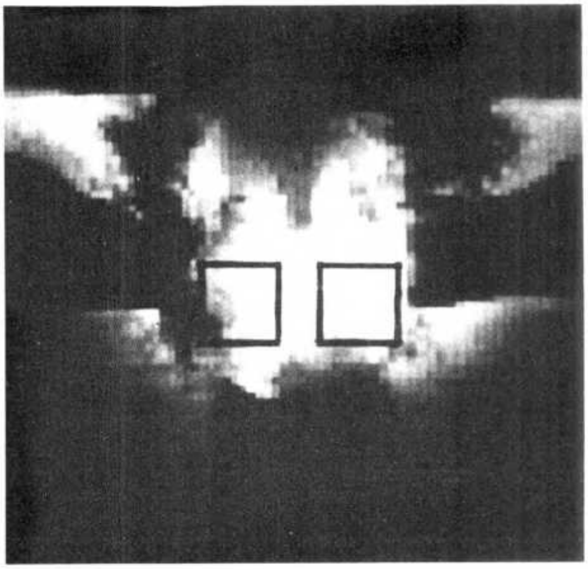

Fig. 2 Template attached to the monitor screen showing an infra-red scrotal thermogram of a patient with a varicocele. The template was positioned to overlie symmetrically the anterior aspects of the testes. The dimensions of each square were 8 mm and the interval between was 4 mm.

Table 1 Results of Semen Analysis Correlated with Internal Spermatic Vein Reflux, Doppler Grades and Scrotal Temperature

Venography Study (16 Varicoceles)

Left internal spermatic vein reflux	*Number (fertile)*	**Sperm density (m/ml) geometric mean; range*
Present	10 (0)	4.8; 0.1-45.2
Absent	6 (1)	47.6; 28.9-150

* t = 2.68; $P < 0.02$.

Doppler/Thermography Study

Doppler grade	*Number (fertile)*	*Average left scrotal temperature °C*	*Sperm density (m/ml) geometric mean, range*
I	4 (0)	29.9	9.5; 1.6- 58.4
II	14 (4)	30.2	13.7; 0.1-104.1
III	7 (0)	32.3*	9.2; 1.4- 53.4
Controls	12 (6)	30.3	12.3; 0.1-120

* t = 2.83; $P < 0.02$.

aspects of the testes (Fig. 2). The template was outlined using the tracker point system and the computer instructed to calculate the average and maximum temperatures within each outline corresponding to the anterior aspect of each testis.

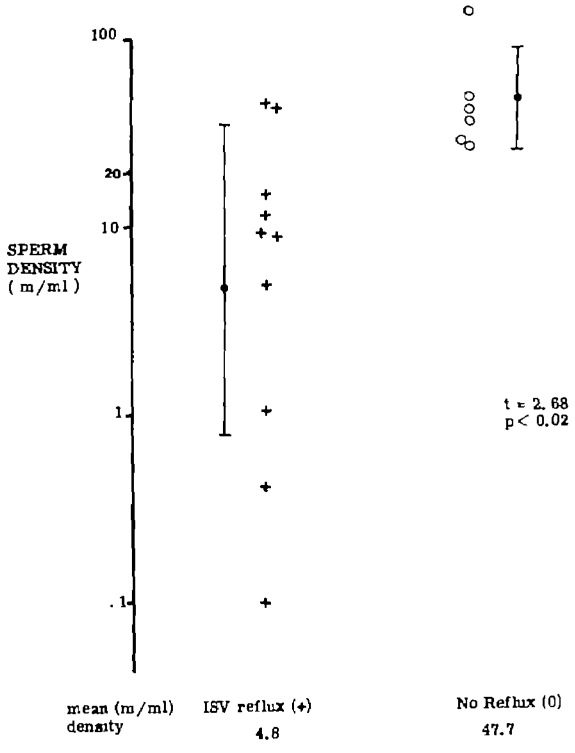

Fig. 3 Relationship between sperm density and ISV incompetence in 16 infertile men with clinical varicoceles.

The template was made so that it would overlie similar areas on all thermograms and the method was found to give reproducible results. It was found by calibration with test objects that the equipment had an accuracy of 0.1°C and the computed surface temperatures were constant between distances of 40 and 100 cm. In some patients 2 or 3 separate thermograms were obtained and the arithmetic means of computed temperatures were used for the calculations.

Each patient provided 2 or more semen specimens by masturbation after 3-day periods of abstinence and the sperm density was assessed by standard techniques using a haemocytometer. The geometric mean of the sperm densities of all available samples from an individual was used for the calculations.

Results

Venography

Sixteen husbands of infertile marriages (sperm density, geometric mean 10.8 m/ml) and one man of proven fertility (sperm density 150 m/ml) underwent transfemoral left renal venography. All had left-sided varicoceles except one infertile patient (sperm density 6.7 m/ml) who was investigated because subclinical reflux had been detected by Doppler (grade II).

Ten patients with varicoceles had incompetence of the junction between the left internal spermatic and renal vein which was more easily demonstrated in the 60° feet down position (Fig. 1a).

Table 2 Correlation Between Doppler Grades and Computed Scrotal Temperatures

Group	*Doppler grade*	*Number (subclinical)*	*Scrotal temperatures °C (mean-standard deviation)*			
			Average values		*Maximum*	
			Right	*Left*	*Right*	*Left*
Left varicocele	I	4	29.9±0.7	29.9±0.9	30.9±0.3	31.3±0.8
	II	14 (1)	30.2±0.8	30.2±1.0	31.5±0.7	31.8±1.0
	III	7 (1)	31.2±1.4	32.3±2.1 ($P<0.02$)*	32.8±1.4	33.7±2.2 ($P<0.01$)*
All varicoceles		25 (2)	30.4±1.1	30.8±1.6	31.8±1.1	32.3±1.6
Controls (no varicocele)		12	30.5±0.8	30.3±1.0	31.7±1.2	31.4±1.2

* Probability values are the results of comparison by Student's t test with the control group.

Seven patients had competent internal spermatic veins at all instances throughout the examination (Fig. 1b).

Doppler assessment had shown all 3 grades. Internal spermatic vein reflux was present in one patient with grade I and the 4 patients with grade III varicoceles; however, it was demonstrated in only 5 of the 12 patients with grade II reflux. The Doppler assessment gave no clear indication of the absence of internal spermatic vein reflux in 7 of the grade II patients and it is of interest that this group included the patient with subclinical reflux and the man of proven fertility.

In the 16 patients with a clinical varicocele the mean sperm density was significantly lower in those patients with incompetent internal spermatic veins (Table 1). The mean sperm density in those patients with reflux was 4.8 m/ml whereas in those with a competent internal spermatic vein the mean density was 47.6 m/ml (Fig. 3).

Thermography

This was performed in 37 patients which included a control group of 12 patients without clinical varicoceles and with a negative Doppler examination for subclinical reflux. The control group consisted of 6 men of proven fertility (mean sperm density 56.1 m/ml) and 6 infertile patients (sperm density 2.0 m/ml). Twenty-three patients had a left-sided clinical varicocele and 2 patients had subclinical reflux as detected by the Doppler technique (grade II and grade III). Four of the patients with varicoceles were of proven fertility (mean sperm density 60.2 m/ml) and the remaining 21 were the husbands of infertile marriages (sperm density 8.4 m/ml). The average and maximum temperatures over both testes were assessed in both groups and the results are shown in Table 2.

The average left scrotal temperature was higher in patients with varicoceles (mean 30.8°C) when compared with the controls (30.3°C), but the difference was not significant and there was no elevation of the average temperature of the right side.

Doppler examination showed a trend towards increased bilateral scrotal temperatures with advancing Doppler grade even though all detected reflux was left-sided. Only grade III varicoceles, including one patient with subclinical reflux, were associated with appreciable elevations of bilateral scrotal temperatures but the elevation was significant on the left side only. Similar results were obtained when maximum scrotal temperatures were compared between Doppler graded varicoceles and controls. When the temperature differences between left and right sides were calculated for each patient it was apparent that grade III varicoceles had significantly higher gradients ($P < 0.01$) relating to both maximum and average temperatures compared with controls. The largest gradient observed was 2.6°C.

There was no significant difference in the sperm densities (geometric means) associated with varicoceles of different Doppler grades when compared with controls even though grade III varicoceles were hotter. This statement applied whether the men of proven fertility were included or excluded from the groups (Table 1).

Venous Flow in the Varicoceles of Fertile and Subfertile Men

The distribution of Doppler grades was found to differ between the varicoceles of 57 infertile husbands and 39 fertile men (Table 3). Spontaneous venous reflux (grades II and III) was demonstrated in 88% of the subfertile and 54%

Table 3 The Distribution of Doppler Grades Observed in the Varicoceles of 39 Men of Proven Fertility and 57 Male Partners of Infertile Marriages

Doppler classification of varicocele	*Fertile (39 men)*	*Infertile (57 men)*
Grade I	18 (46%)	7 (12%)
Grade II	14 (36%)	29 (51%)
Grade III	7 (18%)	21 (37%)

$\chi^2 = 9.83$; $P < 0.01$.

The incidence of grade I varicoceles was higher in men of proven fertility ($P < 0.001$) and the incidence of grade III varicoceles was greater in the male partners of infertile marriages ($P < 0.05$).

of the fertile subjects ($P < 0.001$). The incidence of grade III varicoceles in infertile husbands (37%) was twice that in fertile men (18%, $P < 0.05$).

Discussion

The relationship between the varicocele and fertility remains obscure, but there is general acceptance of the benefit of internal spermatic vein ligation in the treatment of infertile men with varicoceles. In 1962 Hanley and Harrison reported 8 recurrences (20%) after this operation and concluded that some varicoceles were caused by incompetence of the cremasteric veins alone. Hendry *et al.* (1973) regarded incompetence of the cremasteric system as secondary to incompetence of the internal spermatic vein. Hill and Green (1977) were able to demonstrate radiologically significant internal spermatic vein reflux in 58% of varicoceles and reflux in their remaining patients was presumably due to incompetence of the cremasteric or other well recognised venous collaterals (Ahlberg *et al.*, 1966). The complexity of venous communications with the spermatic cord may explain the frequent occurrence of subclinical Valsalva induced reflux reported in other Doppler studies (Greenberg *et al.*, 1979; Hirsh *et al.*, 1980).

In the present study the association of a reduction in sperm density with those varicoceles in which internal spermatic vein reflux was demonstrated supports MacLeod's hypothesis (1965) that refluxing adrenal or renal metabolites have an adverse effect on spermatogenesis. It may also explain the high incidence of varicocele reported in patients with oligozoospermia (Dubin and Amelar, 1971; Greenberg *et al.*, 1978; Cockett *et al.*, 1979). In patients with a varicocele and competence of the internal spermatic vein, infertility may be due to other factors as they tended to be associated with higher sperm densities. The present method of Doppler grading was unable to distinguish between competent and incompetent internal spermatic veins.

Davidson (1954) suggested that elevation of testicular temperature might depress spermatogenesis and this has been observed in patients with varicoceles using needle thermocouples, external mercury bulb thermometers and thermography. It is not an invariable finding (Tessler and Krahn, 1966), for in some studies observations were made in the supine posture, often under general anaesthesia, whereas venous reflux is maximal in the erect posture owing to the influence of gravity as demonstrated by the Doppler technique. The different patterns of spontaneous venous activity detected by Doppler equipment have enabled a group of patients with significant elevation of scrotal temperature to be identified, but it should be noted that there was no associated reduction of sperm density. This suggests that any impairment of fertility might be due to another mechanism. Harrison (1966) suggested that epididymal metabolism might be affected and furthermore MacLeod (1969) reported significant improvement in sperm motility, a function conferred on spermatozoa by the epididymis, after internal spermatic vein ligation for varicocele even though there was little associated improvement in sperm density. Other studies utilising thermography in the assessment of varicoceles have been based on the localisation and expansion of hyperthermic areas (Monteyne and Comhaire, 1978) and the most frequently recognised hot area associated with small varicoceles has been the upper part of the left hemiscrotum, which is the anatomical situation of the caput epididymis. The upper left scrotum was the site of Doppler examination of the spermatic cord and the increased incidence of spontaneous reflux in the varicoceles of infertile husbands may be important since these varicoceles tended to be hotter.

The above findings suggest that male partners of infertile marriages with varicoceles, oligozoospermia and internal spermatic vein reflux should be selected for interruption of this venous system, assuming that the depression of spermatogenesis is reversible. The role of incompetence of the other routes of venous drainage of the spermatic cord in the aetiology of male infertility remains undecided. At the present time there is no non-invasive technique capable of distinguishing between the different types of varicocele.

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The Significance of Serum Sperm-Agglutinating Antibodies in Men with Infertile Marriages

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Summary—Three hundred consecutive male partners of infertile marriages had serum samples tested for sperm agglutinating and sperm immobilising antibodies, using a micro-technique: 30.3% were found to be positive. Out of a control group of 100 fertile men 10 had antibodies detected (10%) and these at low titre; this difference was significant.

The results of these serum tests were found to correlate with the results of seminal plasma tests, the mixed antiglobulin reaction for IgG and sperm cervical mucus contact testing, although all of these tests were less discriminatory with regard to fertility. The serum micro-immobilisation test showed a statistical association with fertility when analysed in those couples where both husband's and wife's tests showed no other bar to fertility.

Rumke *et al.* in 1974 reported that the presence of serum agglutinating activity against spermatozoa correlated with decreased fertility. Kremer and Jager (1976) suggested that sticking of sperm to cervical mucus is one mechanism whereby antibodies may interfere with fertility. Hendry *et al.* (1979) treated a series of these patients with steroids and reported 14 pregnancies by 47 men; this pregnancy rate is slightly greater than the 20% usually observed in the wives of men attending an infertility clinic. Doubt has been cast on the significance of these antibodies by Cohen and Gregson (1978), who stated that they may be part of the normal process whereby the female genital tract selects healthy sperm from the millions in the ejaculate.

The advent of micro-techniques allows the analysis of larger numbers of small samples. We have used these techniques in a study of men attending a general infertility clinic and correlated the findings with a well documented history, to try to answer the question—do antibodies exist and do they matter?

Patients

Three hundred consecutive patients attending the infertility clinic at the Western General Hospital, Edinburgh, over a 12-month period had a sample of blood, seminal plasma and spermatozoa tested. In addition, a history was taken by questionnaire and interview. Physical examination and testicular size were documented.

A control group of 100 men attending for vasectomy gave informed consent to the assay of blood and in some cases semen samples before operation. These men had between them 265 children and at the time of testing all had children under 2 years of age.

Materials and Method

Standard techniques were used. Agglutinating antibodies were detected using the tray agglutination test (TAT) (Friberg, 1974). Immobilising antibodies were detected with a complement dependent micro-immobilisation test (MIT) as described by Husted and Hjort (1976). Spermatozoa were tested using the mixed antiglobulin reaction where sperm are incubated with red cells sensitised to immunoglobulin G (Jager *et al.*, 1978). This test depends on sperm motility and was not possible when either density or motility was very poor. Sperm cervical mucus contact tests were carried out using the wife's pre-ovulatory cervical mucus; this test again depends on good motility (Kremer and Jager, 1976). A shaking non-progressive movement was regarded as a positive test.

Results

Serum Antibodies (Table 1)

A total of 300 clinic patients and 100 fertile

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Serum Agglutinating Activity in Patients and Controls

Pregnancy record	*Negative*	*Serum TAT titre*									
		4	*8*	*16*	*32*	*64*	*128*	*256*	*512*	*1024*	*2048*
1 Control	90 (90%)	1	8		1						
2 Now	27 (90%)		1		1	1					
3 Past	33 (70%)		4	1	3	2	4				
4 Never	166 (74%)		8	9	8	6	7	6	6	2	5

Table 2 Seminal Plasma Agglutinating Activity in Patients and Controls

Pregnancy record	*Negative*	*Seminal plasma TAT titre*									
		4	*8*	*16*	*32*	*64*	*128*	*256*	*512*	*1024*	*2048*
1 Control	18										
2 Now	16 (80%)		4								
3 Past	27 (69%)	2	6	3	1						
4 Never	134 (72%)	5	14	5	9	6	7	4	2	1	

controls were examined for serum antisperm antibodies. The results for the tray agglutination test are shown in Table 1 with the patients classified on the basis of their fertility record:

(1) Fertile controls.
(2) NOW, patients whose wives became pregnant during the course of investigation but before any treatment.
(3) PAST, men who have fathered previous children.
(4) NEVER, patients with primary infertility.

The difference in the distribution of titres between controls and groups 3 and 4 was significant (Wilcoxin Rank sum test: $P<0.01$). The currently pregnant group resembled the control group.

The serum micro-immobilisation test (MIT) showed consistently lower titres than the TAT and was positive only in 31% of those patients with positive TAT. None of the controls showed a positive MIT.

Seminal Plasma Antibodies (Table 2)

TAT and MIT were carried out on the seminal plasma of 246 patients and 18 controls. The pattern of results resembled that found for serum TAT. There was a significant tendency to a higher titre in group 4 compared with groups 2 and 3 ($P<0.01$). As with the serum MIT, the seminal plasma MIT showed consistently lower titres than the TAT and was positive in 25% of cases showing a positive seminal plasma TAT.

A strong correlation was found between serum and seminal plasma titres (Fig.). Among those in whom both were positive the titres were within 2 dilutions of each other in 79% of cases; where the titres differed the serum value was higher but the median difference was only one dilution.

Mixed Antiglobulin Reaction (Table 3)

In 228 patients the MAR test was carried out in addition to serum and seminal antibody tests. The percentages of positive and equivocal results in groups 2, 3 and 4 at 13.3%, 21.6% and 16.5% were not significantly different. There was good correlation between the presence of agglutinating activity in the serum or seminal plasma and a positive MAR test especially at higher titres (Fig.).

Sperm Cervical Mucus Contact Test (Table 4)

Specimens were obtained to perform a sperm cervical mucus contact test from 80 couples. In

Table 3 Mixed Antiglobulin Reaction in Patients (I.G.G.)

Pregnancy record	*MAR test technically impossible (low count or low motility)*	*−VE*	*±*	*+VE*	*++VE*
2 Now		13		2	
3 Past	2	27	5	3	
4 Never	37	109	5	22	3

		TAT MIT	TAT MIT	TAT MIT	TAT MIT	TAT MIT	TAT MIT ■	TAT MIT	TAT MIT ■	INCOMPLETE DATA BLOOD RESULTS ONLY
SERUM		+VE +VE	+VE +VE	+VE -VE	+VE -VE	+VE +VE	-VE -VE	+VE -VE	-VE -VE	
SEMINAL PLASMA		+VE +VE	+VE -VE	+VE +VE	+VE -VE	-VE -VE	+VE +VE	-VE -VE	+VE -VE	
SERUM TAT TITRE OR SEMINAL PLASMA TAT TITRE ■	2048	+ + + +	+							
	1024	+			+					
	512		+ +		+ -			E		1
	256	+ + +			+ -					*
	128	*	+ + *		+			12 6 10 * $\boxed{E}\boxed{-}\boxed{-}$	-	5 * $\boxed{1}$
	64	10 + $\boxed{+}$	E		1 - - -			P $\boxed{E}\boxed{-}$		
	32		3.5 + $\boxed{+}$	+ -	P 3 8 * * $\boxed{-}\boxed{1}\boxed{E}$	-		-	-	1
	16			*	3.5 + + + - - $\boxed{-}$		-	- - E	4 4 * $\boxed{-}\boxed{-}$	
	8		+		4 3 P $\boxed{E}\boxed{-}\boxed{+}$ * * + E			7 - * * $\boxed{E}$	P 2 P $\boxed{-}\boxed{+}\boxed{-}$ - - * 1	3 $\boxed{1}$
	4						2 $\boxed{*}$		- E - -	

KEY
+ MAR +VE
- MAR -VE
E MAR EQUIVOCAL
1 MAR NOT DONE

* MAR NOT POSSIBLE
☐ PREGNANCY PAST OR NOW AGE OF CHILD STATED ABOVE IN BOX
P = PREGNANT

Fig. Relationship between the serum agglutination titre, other antibody tests and the fertility state of the 91 out of 300 men tested who had evidence of antisperm antibodies.

Table 4 Relationship Between Sperm Cervical Mucus Contact Test and Other Antibody Tests

Pregnancy record		*Now*		*Past*		*Never*	
Evidence of antibodies on either TAT, MIT or MAR		*No*	*Yes*	*No*	*Yes*	*No*	*Yes*
Findings on sperm cervical mucus contact test	Husband's sperm shaking			1	4	1	21
	Husband's sperm progressively motile	2	1	2	3	16	2
	Sperm sample or mucus sample inadequate	1		1	2	15	8

27 cases the sperm sample on cervical mucus sample was so poor that it was not possible to evaluate the test. This was the case in spite of the fact that each couple was given detailed instruction of the time of the menstrual cycle to attend and free access to the clinic without appointment. The results are shown in Table 4. There was good correlation between a positive serum and seminal plasma TAT and a positive SCMC; the correlation was less clear with other tests. Two couples with no evidence of antisperm antibodies on the husbands' tests nevertheless had positive SCMC; in one case antibodies were detected in the wife and in the other case, despite testing the wife's serum and cervical mucus, antibodies were not detected.

Relationship of Antibody Tests to Fertility

The correlation between the TAT, MIT and MAR test and patients' fertility record is shown in the Figure. A high serum TAT titre was likely to be associated with other positive tests and this group appears to have a poor fertility record. Nine out of 13 couples with serum TAT titre above 1 : 256 had no other explanation for infertility as judged by semen analysis, semen culture, chromosome analysis on both partners and tests for tubal patency and ovulation. Table 5 shows a statistical analysis looking at the pregnancy record in those couples with semen density above 20 million/ml and where the wives had been shown to have patent tubes and ovulation. There is a significant correlation between the serum micro-immobilisation test and the chance of pregnancy using tests for trend in proportions.

Discussion

Ninety-one men (30.3%) from the group of 300 patients had some evidence of antisperm antibodies. This is a larger percentage than usually reported and probably means that the agglutination tests detected a non-immunological phenomenon as well as true antibody. It seems likely that these are the men in the lower right quarter of the Figure, where the MAR test for IgG is negative and most of the pregnancies which occurred fell into this group. Rumke and Hekman (1977) have suggested a beta lipoglobulin may be responsible, although this is usually found when the serum from pregnant women is tested.

This type of study, involving the handling of over 4,000 items of information, is open to many errors; nevertheless, strong statistical evidence emerges that the incidence of antibodies differs markedly between fertile men and infertile men and that,

Table 5 Relationship Between Positive Antibody Tests and Fertility Record (Analysis on Couples Where Wife has Tubal Patency and Ovulation and Husband Semen Density Greater than 20 Million/ml and a Normal FSH (<5.9 μ/l)

	Positive for each test (%)				
	Serum		*Seminal plasma*		
	TAT	*MIT*	*TAT*	*MIT*	*MAR*
Now	13	0	27	0	25
Past	50	10	33	10	56
Never	42	24	50	14	34
No	76	76	64	64	58
Sig.	$P<0.10$	$P<0.05$	N.S.	N.S.	N.S.

Statistical significance from tests for trend in proportions.

when present, these are associated with infertility. It would be interesting to follow this group of patients to see if the poor fertility record for antibody positive patients holds true for a number of years, but this is not practical because treatment is demanded. Preliminary results from steroid treatment are encouraging; a number of positive patients on repeat testing become negative and several after many years of trying have reported their wives pregnant.

We plan to repeat this type of analysis on the next 300 patients and hope to form a clear idea from the total group as to which tests are the most useful. The present work indicates that the serum immobilisation test may have the best prognostic significance. It is rather disappointing that seminal plasma and MAR testing do not seem to be so predictive, since it is much more convenient to apply these tests to routine seminal analysis.

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The Investigation of Organic Impotence

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Summary—A proportion of impotent men may have one or more underlying organic causes for their impotence and might benefit from the implantation of a silastic penile prosthesis. In order to identify those men with organic impotence we have investigated 30 impotent men. The methods used have included the assessment of penile arterial perfusion by techniques involving a Doppler probe, nocturnal penile tumescence studies, cystometry and cavernosography. Despite the limitations of these various techniques their combined use may help in the recognition of organic impotence and thus facilitate its treatment.

Impotence may be defined as the inability to obtain or sustain a penile erection for the purpose of coitus. Although studies of human sexual behaviour have suggested that impotence often has a psychogenic basis (Masters and Johnson, 1970), there is an ill-defined group of men who have an underlying organic reason for their disability (Shrom *et al.*, 1979). Such patients may benefit from surgical treatment.

In an attempt to identify those factors which contribute to organic impotence we have studied a selected group of men referred to the St Peter's Hospitals between September 1979 and April 1980.

Patients and Methods

The patients' ages ranged from 21 years to 66 years with an average age of 45 years.

All were seen initially in the out-patient clinic, where the first interview served to gather the main points of the presenting history and to establish a rapport. Attention was particularly paid to the speed of onset of the impotence, the presence or absence of erections on waking from sleep and the nature of any previous illness, operation or drug treatment.

During the ensuing physical examination, particular note was made of the distribution of body hair and body fat, the blood pressure and state of the peripheral pulses and the presence of any abnormality of the genitalia. A full neurological examination was performed in all cases.

At this first attendance blood was taken in order to exclude the presence of anaemia, renal failure or an underlying hormonal abnormality. A urine specimen was examined for abnormal constituents.

Each patient was subsequently admitted to hospital for further investigations.

In the first of these an 8 MHz Doppler probe was used to locate the pulsations of the penile arteries. Six pulses were sought—the paired superficial and deep penile arteries at the base of the shaft of the penis and the 2 frenular arteries distally. The number of arteries identified in each case was recorded.

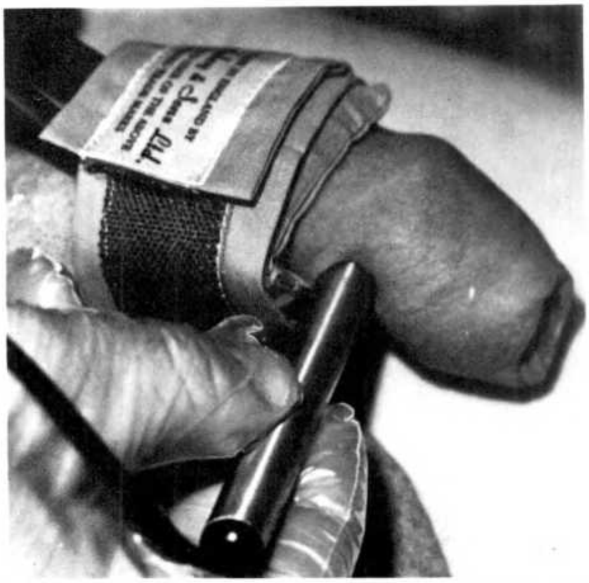

Fig. 1 2.5 cm paediatric sphygmomanometer cuff being used to measure the penile systolic blood pressure. A Doppler probe is placed distally on the penis.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

The Doppler technique was also used to assess the difference between brachial and penile systolic blood pressures (Abelson, 1975). The brachial pressure was first measured using a standard sphygmomanometer cuff. The penile pressure was then taken with the help of a 2.5 cm paediatric cuff placed proximally around the penile shaft and a Doppler probe placed either over one of the frenular arteries or on the glans of the penis (Fig. 1). Any difference between the systolic blood pressure at the 2 sites was noted.

During the night following admission to hospital the patients were monitored to see whether or not they experienced the periods of penile tumescence which normally occur during sleep (Karacan *et al.*, 1966). Fine mercury strain gauges were first constructed by filling loops of 1 mm diameter silastic tubing with mercury (Karacan, 1969). Two of these gauges were then placed so as to encircle the penile shaft and were attached to a 2-channel chart recorder via a Wheatstone bridge circuit and amplifier (Karacan, 1969). Penile tumescence therefore caused stretching of the gauges which in turn led to a change in the electrical resistance of the mercury columns. These changes were recorded as deflections on the chart. Calibration of the gauges was achieved by means of a graduated, adjustable template. The recordings were repeated on subsequent nights where thought necessary.

On the following morning a glucose tolerance test (GTT) was performed, during the course of which each patient was asked to fill in a questionnaire. At the conclusion of this test an ECG recording was made, followed by a cystometrogram (CMG). Subsequently cavernosography was performed on 10 men who complained of the brevity of their weak erections.

Results

Nineteen of the men were categorised as suffering from organic impotence and 11 from psychogenic impotence.

History and Examination

In the organic group where no major operation or injury had occurred to explain a sudden onset of impotence, 8 of 11 men had had a gradual onset of the disability (Table 1). In the psychogenic group 7 of 11 such men had a sudden onset of impotence.

Twenty-six of the 30 men complained of partial and/or disablingly brief erections. Only 2 men in each group reported no erections at all. Erections present on waking generally matched the erections achieved by sexual arousal in the organic group, but 5 of the 11 men in the psychogenic group reported full erections on waking.

Table 1 The Speed of Onset of Impotence within the Group

Onset	*Organic*	*Psychogenic*
Sudden	1	7
Sudden + major trauma/illness	8	—
Gradual	8	3
Always present	2	1
Total	19	11

Seventeen of the 19 members of the organic group had a prior history of illness or trauma likely to explain their impotence (Table 2). Four of the other 11 men in the psychogenic group related the onset of their problem to a minor operation or traumatic incident.

Four of the organic group were on antihypertensive drugs which have been reported as causing impotence. One of the psychogenic group had a short history of alcoholism but normal liver function studies.

Abnormal neurological studies were found in

Table 2 Previous Medical History

Previous medical history	*No.*
Vascular disease Atheroma (5) Priapism (1)	6
Endocrine disease Diabetes mellitus (3) Hyperprolactinaemia (1)	4
Neurological disease Disseminated sclerosis (1) Neurosyphilis (1)	2
Peyronie's disease	1
Trauma (major) Radical pelvic operation (2) Pelvic fracture (1) Penile injury (1)	4
Trauma (minor) Circumcision (2) Penile trauma (1) Injection of piles (1)	4
Nil	9
Total	30

Table 3 Summary of the Findings from the Special Investigations Performed

	Psychogenic (11)	*Organic (19)*
<4 penile arteries identified	1	9
>40 mmHg brachial/ penile BP difference	0	7
Weak or absent NPT	0	19
"Unstable" CMG	3/11	11/16
GTT diabetic	0	6
Hyperprolactinaemia	0	2

10 of the organic group. Two were hypertensive, one had abnormal peripheral pulses and another the penile plaques of Peyronie's disease. Two of the men in the psychogenic group appeared mentally unstable.

Special Investigations

All men had normal levels of haemoglobin and creatinine. Three of the 30 men were known diabetics and so the GTT was not repeated. Three other members of the organic group were found to be diabetic as a result of this test. Three men had raised levels of serum prolactin, although one was only just in the abnormal range. One was known to have hyperprolactinaemia and had stronger erections whilst taking bromocriptine. All had normal levels of other sex hormones. No other hormonal abnormalities were detected.

Nine of the 19 men with organic impotence had less than 4 detectable penile pulses (Table 3) whilst 10 of the 11 in the other group had 4 or more pulses audible with the Doppler probe. Seven men had a penile systolic blood pressure more than 40mmHg below the level of their brachial pressure. All were in the organic group and 6 of the 7 had less than 4 pulses on Doppler examination.

A total of 52 nocturnal tumescence recordings were made. Ten were discarded as being technically unsatisfactory. All men in the psychogenic group had normal tracings (Fig. 2). Twelve of the organic group had weak erections and 6 had none at all. In these instances the recordings were repeated.

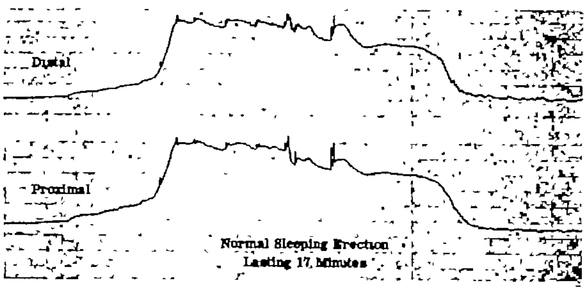

Fig. 2 Recording of a normal period of nocturnal tumescence.

CMGs were performed on 27 of the 30 men. Eleven of 16 men in the organic group had unstable bladders as judged by the presence of unstable detrusor contractions whilst filling or an end filling pressure of more than 20 cm H_2O.

Eight cavernosograms were normal; one showed evidence of Peyronie's disease and another demonstrated a patent shunt between the corpora cavernosa and a saphenous vein, formed initially as treatment for an episode of priapism.

Discussion

Medical interest in the mechanisms and treatment of organic impotence has increased in recent years. This is due to the impetus provided by the work of Masters and Johnson (1970) on sexual dysfunction, the introduction and success of semi-rigid penile prostheses and changes in sexual attitudes.

The Doppler probe has been used by several investigators to assess the arterial blood flow to the penis (Malvar *et al.*, 1973). Whilst the superficial penile arteries are relatively easy to detect if present, the deep arteries sometimes cannot be detected in normal men. As it is the flow through these deep vessels to the corpora cavernosa which seems of most relevance in relation to the haemodynamics of erection, a test of the patency of these deep vessels seems to be required for the better assessment of states of organic impotence. The comparison of brachial and penile systolic blood pressures has been used as an index of penile arterial perfusion (Gaskell, 1971; Abelson, 1975) and a difference of more than 40 mmHg has been shown to be related to impotence in men with vascular disease (Barry and Hodges, 1978). Unfortunately this test also measures the blood pressure in the superficial penile vessels and may not accurately represent the flow pattern of the cavernous arteries.

Nocturnal penile tumescence monitoring was introduced by Karacan, the suggestion being that men with psychogenic impotence have normal erections during sleep, whilst those with organic impotence have inadequate erections during sleep which correspond to their waking performance. Not only may this proposition be invalid but the technique is cumbersome, time-consuming and prone to experimental error due to body movements of the patient while asleep. These may be minimised by the use of 2 strain gauges, placed proximally and distally respectively on the penis (Casey, 1979). More recently postage stamps have been used as an all or none assessment of the presence of tumescence (Barry *et al.*, 1980).

Ellenberg (1971) has demonstrated that 90% of a group of 41 impotent diabetics had abnormal cystometrograms compared with 10% of 30 potent diabetics. We have also found a high percentage of men with unstable bladders (52% of those tested) but the significance of this is questionable.

Cavernosography is a minor procedure which can be performed under a local anaesthetic in the radiology department. Several reports have recently appeared of impotent men who have been shown to have an abnormal venous drainage of the corpora cavernosa (Ebbehøj and Wagner, 1979). Correction of the anomaly has sometimes resulted in a return of potency. One man in this present series had an iatrogenic communication of this kind between the corpora cavernosa and saphenous vein, formed initially as treatment for priapism; the closure of this shunt proved unsuccessful in reversing his impotence.

A number of centres have been performing internal iliac arteriography in selected cases of organic impotence, prior to attempting operative revascularisation of the corpora cavernosa with microvascular techniques. So far this latter procedure appears to have limited success and we feel therefore that there is seldom an indication for this invasive form of investigation.

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Penile Prostheses for the Treatment of Impotence

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Summary—Eighty-nine patients were treated for impotence with penile prostheses. The Small-Carrion prosthesis was used in 56 patients, the inflatable prosthesis in 27 and Pearman's prosthesis in 6 patients. The overall functional results with the Small-Carrion and inflatable prostheses were comparable.

World-wide experience with the penile prosthesis is less than 2 decades old. The current surgical treatment of impotence has progressed significantly since early attempts at utilising segments of rib cartilage and tube skin grafts. Since the first successful attempt at implanting tissue-compatible acrylic into a patient with organic impotence (Goodwin and Scott, 1952), a variety of materials has been used (Loeffler and Sayegh, 1960; Loeffler *et al.*, 1964; Beheri, 1966). Pearman (1967, 1972) developed the first silicone prosthesis, which he placed dorsally between Buck's fascia and the tunica albuginea. Scott *et al.* (1973) have developed a prosthesis of dacron-reinforced silicone rubber which is inflatable. Small *et al.* (1975) described a penile prosthesis consisting of a medical-grade silicone exterior with silicone sponge interior. Later, other types of semi-rigid prostheses were described, but they were not as popular as the inflatable and Small-Carrion prostheses.

Broadly speaking, the 2 types presently available are semi-rigid rods and inflatable prostheses. Their overall functional success is approximately 90%. The cost, complications and satisfaction vary between semi-rigid and inflatable prostheses. We present our experience with the different types of penile prosthesis.

Materials and Methods

We have treated 89 patients for impotence: 56 of these patients received Small-Carrion prostheses, 27 received inflatable prostheses and 6 received Pearman's prostheses.

Table 1 Age of Patients

20-30	6
31-40	10
41-50	18
51-60	32
61-70	23

Patient Selection

Most of the patients had organic causes for impotence, although some whose impotence was psychogenic but who were refractory to psychotherapy were selectively accepted. Six patients with Peyronie's disease had Small-Carrion prostheses for correction of curvature of the penis. All patients received a complete medical examination and relevant laboratory data were collected preoperatively. The patients' ages ranged from 20 to 70 years (Table 1). Eighty-six patients were Caucasian, 2 black and one American Indian. The duration of impotence varied from 6 months to 5 years or more (Table 2).

The aetiological factors causing erectile impotence are noted in Table 3. In 79 patients the cause of impotence was clearly established. The main organic pathology was radical surgery for prostatic carcinoma, followed by diabetes. In 10

Table 2 Duration of Impotence

Less than 1 year	7
1 year	19
2 years	22
3 years	14
4 years	5
5 years of more	19
Unknown	3

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 3 Causes of Impotence

Cause	*Number of patients*
Prostatic carcinoma	24
Radical prostatectomy—18	
Perineal cryosurgery—6	
Diabetes mellitus	22
Peyronie's disease	6
Neurogenic disease	6
Pelvic and perineal injury	5
Priapism	4
Vascular disease	3
Abdominoperineal resection	3
Cause undetermined	10
Total	89

patients the cause of impotence was unknown; this group included psychogenic causes. The duration of follow-up varied from one to 5 years. All of the patients with 5-year follow-up had Pearman's penile prostheses.

The operative technique used in the installation of the inflatable prosthesis was described by Scott *et al.* (1973) and subsequently modified by Furlow (1978a, b). The Small-Carrion prosthesis was implanted either perineally, as initially described by Small *et al.* (1975), or by infrapubic or circumcision incision.

Pre-operative preparation, operative care and post-operative management, including antibiotics to prevent infection, were used as described previously (Small and Carrion, 1975; Small, 1978). The patients were advised not to use the penile prosthesis for intercourse for a period of 4 weeks post-operatively.

Results

Eighty-nine patients with impotence underwent insertion of penile prostheses and were followed for at least one year post-operatively. Pearman's prosthesis was used only before 1975.

Fifty-six patients received Small-Carrion prostheses. In 4 patients the prosthesis was removed—in 2 for pain, one for infection and another for replacement with an inflatable prosthesis. In 3 patients the prosthesis eroded—in one case through the glans penis and in the other 2 through the urethra (Table 4).

Table 4 Complications of Small-Carrion Prosthesis

Erosion	3
Urethral—2	
Glans penis—1	
Removed	4
Deep infection	1
Superficial infection	2
Incorrect position	5
Post-operative pain	11
Cold penis	2
Intermittent catheterisation	2
Transurethral resection prostate	1

Eleven patients with Small-Carrion prostheses complained of post-operative pain. Two patients had their prostheses removed for pain—one after 3 months and the other after 6 months. Post-operative pain was usually managed with mild analgesics and lasted as long as 4 weeks in some patients. Infection was seen in 3 patients—in 2 a superficial infection healed spontaneously, and the other needed removal of the prosthesis for deep infection. In 5 patients the prostheses were found to be in an incorrect position (one rod longer than the other), but the functional results were good in all except one patient in whom the prosthesis was replaced with a longer one. Two patients complained of cold penis. Two patients needed intermittent catheterisation for increased residual urine after the placement of their prostheses. One patient needed transurethral resection of the prostate, which was achieved through perineal urethrostomy. In 2 patients we failed to place the Small-Carrion prosthesis intra-operatively because of perforation of the tunica albuginea. These 2 patients are not included in the overall series.

Forty-eight patients with Small-Carrion prostheses have been followed for one or more years. All are satisfied with their prosthetic devices except one patient for whom we do not have proper follow-up. The functional success rate is approximately 88% (Table 6).

Inflatable Prosthesis

Twenty-seven patients received inflatable prostheses. The long-term functional success rate is approximately 95% (Table 6). The device was

Table 5 Complications of Inflatable Prosthesis

Post-operative pain	4
Tube kinking	3
Ruptured cylinder	3
Leakage of fluid	2
Broken tubing	1
Malfunction of pump	1
Insufficient fluid	1
Ballooning of cylinder	1
Deep infection	1
Intermittent catheterisation	1

Table 6 Satisfaction

	Small-Carrion	*Inflatable*	*Pearman's*
Satisfactory	48	26	1
Unsatisfactory	7	1	5
Unknown	1	0	0
Total	56	27	6

removed for infection in one case. Complications, mainly of a mechanical type, were seen in a number of patients (Table 5). In 3 cases the cylinders ruptured, needing replacement. In 3 cases tubing kinked, necessitating operative correction. Four patients complained of pain during the immediate post-operative period; this pain was controlled by analgesics. A few patients complained of scrotal discomfort at the site of the pump.

Discussion

Impotence has been a diagnostic as well as a management problem, since in most cases no effective form of medical therapy exists. Penile prostheses are widely used for the management of organic and, in some cases, psychogenic impotence. Both the inflatable as well as the Small-Carrion prostheses appear to be satisfactory methods of treating impotence. However, both prostheses have distinct advantages and disadvantages which must be considered and discussed with the patient before a selection is made.

The aetiology of erectile impotence is generally ascribed to either organic or psychogenic causes. The common causes of organic impotence can be divided into inflammatory, traumatic, neurological, endocrine, vascular, congenital, neoplastic and metabolic, as well as those related to various drugs. In this present series the commonest cause of impotence was surgery for prostatic carcinoma. In other reported series the commonest cause was diabetes mellitus.

The key to the diagnosis of erectile impotence is a full history and physical examination. The history should contain a complete review of symptoms with special emphasis on neurological, endocrine and genitourinary features.

The physical examination should include a complete neurological assessment if disease is suspected. Vascular pulses must be checked, especially in the femoral and posterior tibial region. Psychological screening may be necessary in the early detection of unsuitable candidates for surgery.

The treatment of impotence with the Small-Carrion prosthesis and the inflatable prosthesis has a substantial success rate (Table 6). However, both prostheses present distinct advantages and disadvantages. In the Veterans Administration Hospital only semi-rigid prostheses are available, but the satisfaction rate does appear to be comparable with that of patients with inflatable prostheses. The appearance of the penis is not related to the degree of satisfaction. The predominant advantage of the Small-Carrion prosthesis is lack of mechanical parts to go wrong. This prosthesis is cheaper and the simplicity of insertion is also an advantage. Initially we used the perineal approach to implant the prosthesis but later found an infrapubic approach and circumcision incision gave equally good results. The main limitation for the Small-Carrion prosthesis is a permanent erection. Rigidity cannot be varied, or length or girth of the penis. Erosion can result from constant pressure, as happened in 3 patients. In addition, an endoscopic operation is difficult because of fixed penile length. In 4 cases the prosthesis was removed—in 2 for pain, one for infection and another for replacement with an inflatable prosthesis.

The predominant asset of the inflatable prosthesis is a natural-appearing erection. The degree of rigidity can be varied with the diminished chance for erosion of the urethra or glans penis. The flaccid penis allows for an endoscopic operation when necessary, while presenting a normal appearance in public places. Some authors have reported that sexual partners are not aware of the prosthesis (Malloy *et al.*, 1980). One of the disadvantages of the inflatable prosthesis is mechanical failure, the incidence of which has varied from 10 to 35% in various studies (Malloy and Von Eschenbach, 1977; Furlow, 1978a, b, c; Malloy and Wein, 1978). Other drawbacks are greater expense and exacting surgical technique. In our series all of the failures were mechanical except for one case of infection. The newer modification of the reservoir and the cylinder should decrease the mechanical complications.

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Prizes and Awards

British Association of Urological Surgeons: Annual Meeting Liverpool. 25-27 June 1980

President: Professor J. P. Mitchell

St Peter's Medal

At the Annual Dinner the President presented the St Peter's Medal to Mr J. H. Johnston of Liverpool, after a citation given by Mr D. Innes Williams.

Berk Pharmaceuticals Lecture

This Guest Lecture, entitled "Genesis and resolution of urinary tract infection", was given by Professor Francis O'Grady, Foundation Professor of Microbiology, University of Nottingham.

C. R. Bard Award

This prize is given to the author who, in the opinion of a panel nominated by Council, has presented the best paper at the Annual Meeting; it consists of a cheque for £250 and a Silver Medal. The prize was awarded to Mr K. F. Parsons for the paper entitled "Endoscopic biopsy in the diagnosis of peripheral denervation of the bladder" by K. F. Parsons, A. G. Scott and S. Traer.

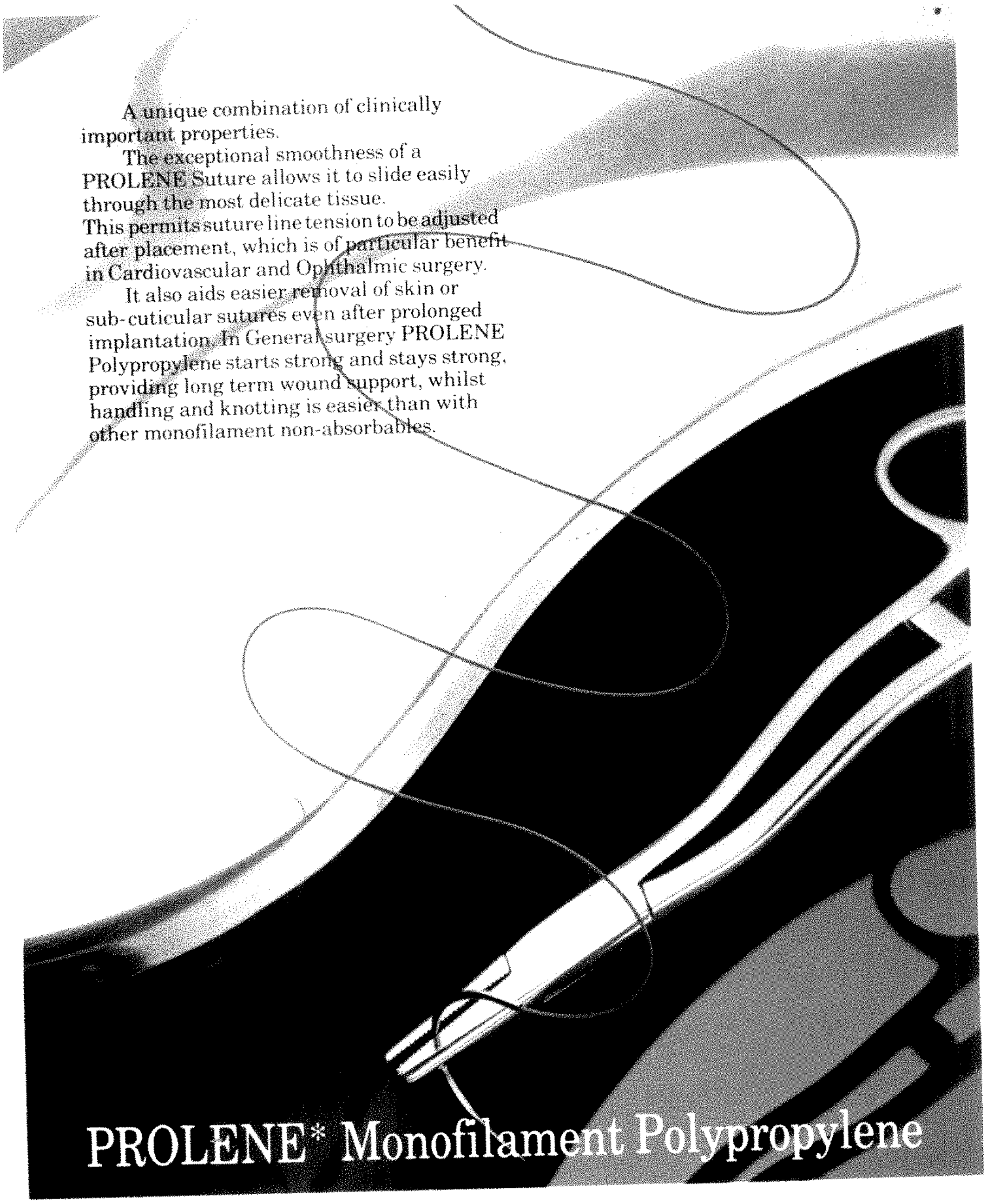
Eschmann Prize

This prize for £150 for the best Scientific Exhibit was awarded to Mr J. E. A. Wickham and Mr J. M. Fitzpatrick for their board demonstration "Nephrolithotomy—renal access".

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £500 for the best article in each volume of the *British Journal of Urology*, provided that it is of outstanding merit. Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia, or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prize winner must submit a programme of visits to Urological Centres outside Britain for consideration by the Council.

No award was made for 1979.



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